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CASE REPORT

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A case of tongue swelling after S-1, oxaliplatin, and trastuzumab for HER2-positive gastric cancer

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Abstract

Background We report a case of a patient with HER2-positive gastric cancer with marked tongue swelling during the second cycle of S-1, oxaliplatin, and trastuzumab.

Case presentation The patient was a 74-year-old male, who was taking an angiotensin II receptor blocker (ARB) for pre-existing hypertension, with no history of allergies, diagnosed with HER2-positive gastric cancer, treated with tegafur, gimeracil, and oteracil potassium (S-1) and oxaliplatin for the first cycle, and trastuzumab was added from the second cycle. Three weeks after initiation, during an outpatient visit, grade 2 oral mucositis and significant enlargement of the patient's tongue were observed. Due to the risk of airway obstruction, the patient was referred to an otolaryngologist. After examination, hereditary angioedema was ruled out, and treatment was discontinued in view of ARB-induced angioedema. However, the tongue swelling did not improve markedly. Considering disease progression due to the discontinuation of chemotherapy, it was decided to change S-1 to capecitabine and continue treatment, and chemotherapy was resumed.

Conclusions Angioedema has been reported to be hereditary and drug-related, and angiotensin-converting enzyme (ACE) inhibitors and ARBs have also been reported to lead to drug-related adverse events. Since the patient had oral mucositis at the time of onset and was taking an ARB, it is thought that oxaliplatin and S-1(SOX), and trastuzumab during ARB therapy induced oral mucositis, leading to the development of angioedema.

Keywords HER2-positive gastric cancer, Angioedema, Oral mucositis, Chemotherapy, S-1, Oxaliplatin, Trastuzumab, Angiotensin II receptor blockers, Candesartan

Background

Japanese gastric cancer treatment guidelines recommend using a combination of trastuzumab cisplatin, plus 5-FU or capecitabine, trastuzumab oxaliplatin plus capecitabine (CapeOX), or S-1 (tegafur, gimeracil, and oteracil potassium) (SOX) to treat HER2-positive unresectable or advanced recurrent gastric cancer (Japanese Gastric Cancer Association 2023). Angioedema has not been reported as an adverse event from chemotherapy. We report the case of a patient with HER2-positive unresectable gastric cancer where a significant tongue

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enlargement occurred during the second cycle of SOX and trastuzumab.

Case presentation

A 74-year-old man with a medical history of hypertension for over 10 years, hyperuricemia, stroke, and prostate enlargement was diagnosed with HER2-positive gastric cancer with liver metastases. The patient was being treated for hypertension with candesartan and amlodipine. The patient had no history of allergic reactions to medications or substances. During the first cycle of chemotherapy, the patient received SOX (S-1 100 mg/d on days 1–14 and oxaliplatin 100 mg/m^2 on day 1) on an inpatient basis, and only grade 1 oral mucositis and constipation grade 1 were detected according to the National Cancer Institute's Common Terminology Criteria for Adverse Events version 5.

For the second cycle of chemotherapy, SOX and trastuzumab (8 mg/kg on day 1) were administered on an outpatient basis. On day 22, at the time of the outpatient visit, the patient had developed oral mucositis grade 2 and constipation grade 2. Additionally, the patient complained of a markedly enlarged tongue and dysarthria for 1–2 weeks (Fig. 1). No abnormalities were observed in blood tests and biochemical tests (Table 1), and there were no other issues with the patient's general condition. The patient was taking allopurinol, candesartan, amlodipine, propiverine, sodium ferrous citrate, magnesium oxide, vonoprazan, sodium ferrous citrate, and daikenchuto. Physical examination revealed the following vital signs: blood pressure was 137/73 mmHg, heart rate was 70 bpm, body temperature was 36.3℃, and peripheral oxygen saturation was 98% while breathing room air. The patient presented with marked enlargement of the tongue and painful oral mucositis, but there was no urticaria. No new medications had been initiated, and the patient reported no ingestion of allergenic foods or other allergenic substances. Thereafter, the patient was seen every week as an outpatient to monitor the progression of tongue swelling; however, there was no worsening or improvement observed.

Table 1 Laboratory data on day 22 of SOX and trastuzumab treatment

Laboratory data	
WBC	3600/μL
ANC	2131/μL
ALC	785/μL
EOS	342/μL
Hb	805 g/dL
PLT	12.6*10^4/μL
Cr	1017 mg/dL
tBil	0.4 mg/dL
AST	28U/L
ALT	28U/L
Na	143 mEq/L
K	4.9 mEq/L
CRP	0.2 mg/dL
LDH	268U/L
ALB	3.5 g/dL

WBC, white blood cell count; ANC, absolute neutrophil count; ALC, absolute lymphocyte count; EOS, absolute eosinophil count; Hb, hemoglobin; PLT, platelet count; Cr, serum creatinine; tBil, total bilirubin; AST, aspartate aminotransferase; ALT, alanine transaminase; Na, serum sodium; K, serum potassium; CRP, C-reactive protein; LDH, lactate dehydrogenase; ALB, serum albumin

On day 45, the patient was evaluated for hereditary and acquired angioedema as well as thyroid disease (Table 2). Due to the possibility of angioedema caused by candesartan, the attending physician requested the hypertension management physician to discontinue candesartan, which was promptly done. After discontinuing candesartan, there was no exacerbation of tongue swelling, and to continue treatment for gastric cancer, S-1 was changed to capecitabine, and chemotherapy was resumed with capecitabine, oxaliplatin, and trastuzumab. Nine cycles have been performed, and there has been no worsening of tongue swelling.

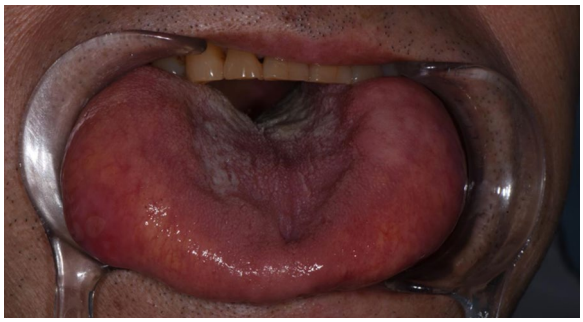

Fig. 1 Tongue swelling observed at the patient's first episode

Table 2 Angioedema-related blood tests on day 45 of SOX and trastuzumab treatment

Angioedema-related blood tests	
C1-inhibitor	100.10%
TSH	1.391μlU/mL
F-T4	0.96 ng/dL
F-T3	2.68 ng/dL
Growth hormone	1.15 ng/dL
ACTH	11.8 pg/mL

TSH, thyroid-stimulating hormone; F-T4, serum free T4; F-T3, serum free T3; ACTH, adrenocorticotropic hormone

The patient has reported some improvement in speech difficulties.

Conclusions

We have reported a case of significant tongue swelling that emerged after the initiation of SOX plus trastuzumab chemotherapy for gastric cancer. There were no reports of tongue swelling associated with oxaliplatin, S-1, or trastuzumab. However, considering its occurrence after the initiation of chemotherapy, we attributed it to chemotherapy-induced effects. Among adverse events other than tongue swelling, Grade 2 mucositis manifested in the oral cavity, which led us to consider its association with tongue swelling. However, even with chemotherapy discontinuation, the tongue swelling did not improve. The patient had pre-existing hypertension and was taking candesartan as an antihypertensive drug, raising the possibility of angioedema caused by angiotensin II receptor blockers (ARBs). However, a considerable amount of time had passed since the initiation of ARB treatment, and even if the angioedema was related to ARBs, we considered it to be influenced by some form of chemotherapy. We hypothesized that chemotherapy-induced oral mucositis served as a triggering factor for ARB-induced angioedema.

Possible causes of an enlarged or edematous tongue include allergic reactions and bradykinin-mediated angioedema (Maurer and Magerl 2021). However, in this case, there was no sudden worsening of symptoms at the time of the visit, no new medications were started or foods ingested, and no symptoms such as urticaria were present, suggesting that an allergic reaction was not likely. Bradykinin-mediated angioedema can be hereditary angioedema, acquired C1 inhibitor deficiency, drug-induced, or idiopathic (Maurer et al. 2022). However, no abnormalities related to C1 inhibitors were observed in this patient. Drug-induced causative agents have been reported in drugs such as penicillin, aspirin, nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors (ACE-Is), ARBs, oral contraceptives, and others (Inomata 2012; Kumar et al. 2022).

Considering that the patient had concurrent hypertension and had been taking an ARB before SOX and trastuzumab therapy, ARB-induced drug-induced angioedema was considered. Angioedema caused by ARBs and ACE-Is has been implicated in bradykinin (Smolinska et al. 2023). The mechanism of the development of vascular edema in ACE-Is is thought to be due to the accumulation of bradykinin (Maurer and Magerl 2021). Increased levels of bradykinin lead to vasodilation, which in turn increases the permeability of endothelial cells, resulting in the swelling of peripheral tissues (Debreczeni et al. 2021). However, although an increase in bradykinin concentration is also observed in ARBs, the mechanism behind this is still largely unknown (Campbell et al. 2005).

The onset of ACE-I and ARB-induced angioedema has been reported to vary from early administration to several years later (Brown et al. 2017). While there have been reports of chemotherapy-triggered angioedema in hereditary angioedema (Morelli et al. 2018), there have been no reports of chemotherapy-triggered angioedema in drug-induced angioedema, such as ACE-I and ARBs, although there have been cases of triggered by dental treatment (Raval 2014).

In this case, the patient did not develop angioedema immediately after starting SOX and trastuzumab but later developed oral mucositis and a swollen tongue, which suggests that the oral mucositis caused by SOX and trastuzumab triggered ARB-induced angioedema and caused the tongue to swell. However, the lack of significant improvement in tongue swelling, in this patient, is inconsistent with previous case reports of angioedema treated with ARBs and ACE-Is, most of which reported rapid improvement in edema symptoms after discontinuation of ARBs and ACE-Is (Konda et al. 2021).

Finally, there is idiopathic angioedema, the cause of which has not been identified. Idiopathic angioedema is thought to be induced by contact with substances or ingestion of food (Sands et al. 2007). However, there have been no reports of chemotherapy being a contributing factor.

This case study suggests that angioedema may be caused by oral mucositis following chemotherapy. Notably, when chemotherapy was resumed, fluoropyrimidine was switched from S-1 to capecitabine. The reason was that capecitabine as reported to cause less oral mucositis than S-1 in a comparison of adverse events between S-1 and capecitabine (Zhang et al. 2021).

In summary, we report a case of significant tongue enlargement after SOX and trastuzumab treatment for unresectable advanced gastric cancer. Angioedema of the tongue, pharyngeal, and laryngeal mucosa can lead to asphyxia with airway obstruction, and caution should be exercised because tongue enlargement may occur due to chemotherapy-induced oral mucositis, as in this case (Pfaue et al. 2019; Mann et al. 2023).

Abbreviations

CapeOX	Oxaliplatin plus capecitabine
S-1	Tegafur, gimeracil, and oteracil potassium
SOX	Oxaliplatin plus S-1
ACE-Is	Angiotensin-converting enzyme inhibitors
ARBs	Angiotensin II receptor blockers
WBC	White blood cell count
ANC	Absolute neutrophil count
ALC	Absolute lymphocyte count
EOS	Absolute eosinophil count

Hb	Hemoglobin
PLT	Platelet count
Cr	Serum creatinine
tBil	Total bilirubin
AST	Aspartate aminotransferase
ALT	Alanine transaminase
Na	Serum sodium
K	Serum potassium
CRP	C-reactive protein
LDH	Lactate dehydrogenase
ALB	Serum albumin
TSH	Thyroid-stimulating hormone
F-T4	Serum free T4
F-T3	Serum free T3
ACTH	Adrenocorticotropic hormone

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Author contributions
TA was a member of the treating team, drafted the manuscript, conducted the literature review, analyzed the patient data, and finalized the manuscript. TS, AT, and IH were members of the treating team and analyzed the patient data. YO was a member of the treating team, and reviewed and edited the final manuscript. TY was a member of the treating team, supervised the case report, and reviewed and edited the final manuscript. EI supervised the project. All authors read and approved the manuscript prior to submission.

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Availability of data and materials
All data used for this report are included in the text.

Declarations

Ethics approval and consent to participate
The case report did not require ethics approval. Consent to participate was obtained from the patient.

Consent for publication
Written informed consent was obtained from the patient for publication of this case report and accompanying images.

Competing interests
The authors declare that they have no competing interests.

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References

Brown T, Gonzalez J, Monteleone C (2017) Angiotensin-converting enzyme inhibitor-induced angioedema: a review of the literature. J Clin Hypertens 19(12):1377–1382
Campbell DJ, Krum H, Esler MD (2005) Losartan increases bradykinin levels in hypertensive humans. Circulation 111(3):315–320
Debreczeni ML, Németh Z, Kajdácsi E et al (2021) What is behind hyperpermeability in bradykinin-mediated angioedema? Clin Rev Allergy Immunol 60(3):318–347
Inomata N (2012) Recent advances in drug-induced angioedema. Allergol Int 61(4):545–557
Japanese Gastric Cancer Association (2023) Japanese Gastric Cancer Treatment Guidelines 2021 (6th edition). Gastric Cancer 26(1):1–25
Konda M, Inoue S, Naito Y et al (2021) Life-threatening airway obstruction caused by angioedema in a morbidly obese postoperative patient: a case report. JA Clin Rep 7(1):1
Kumar N, Kiran M, Gupta K, Pareek S (2022) Telmisartan-induced angioedema: a rare clinical finding. J Fam Med Prim Care 11(7):4026–4028
Mann H, Pandey S, Pokhriyal S et al (2023) Losartan-induced angioedema: a case report. Cureus 15(4):e37818
Maurer M, Magerl M (2021) Differences and similarities in the mechanisms and clinical expression of bradykinin-mediated vs. mast cell-mediated angioedema. Clin Rev Allergy Immunol 61(1):40–49
Maurer M, Magerl M, Betschel S, Aberer W, Ansotegui IJ, Aygören-Pürsün E et al (2022) The international WAO/EAACI guideline for the management of hereditary angioedema-the 2021 revision and update. Allergy 77:1961–1990
Morelli C, Formica V, Pellicori S et al (2018) Chemotherapy in patients with hereditary angioedema. Anticancer Res 38(12):6801–6807
Pfaue A, Schuler PJ, Mayer B et al (2019) Clinical features of angioedema induced by renin-angiotensin-aldosterone system inhibition: a retrospective analysis of 84 patients. J Community Hosp Intern Med Perspect 9(6):453–459
Raval P (2014) A case report looking at ACE inhibitors as the cause of angioedema during dental treatment. Br Dent J 216:73–75
Sands MF, Blume JW, Schwartz SA (2007) Successful treatment of 3 patients with recurrent idiopathic angioedema with omalizumab. J Allergy Clin Immunol 120(4):979–981
Smolinska S, Antolín-Amérigo D, Popescu FD (2023) Bradykinin metabolism and drug-induced angioedema. Int J Mol Sci 24(14):11649
Zhang Q, Qian Y, Yin Y (2021) Comparison of S-1-based vs capecitabine-based adjuvant chemotherapy for patients with gastric cancer: a systematic review and meta-analysis. Eur J Clin Pharmacol 77(12):1791–1804

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