

# Carbamazepine Induced Angioedema Mimicking Radiation Induced Edema in a Patient with Trigeminal Neuralgia and Squamous Cell Head and Neck Cancer.

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## Introduction

Carbamazepine is a commonly used anticonvulsant drug considered first-line therapy in the treatment of trigeminal neuralgia [5,14]. It has known cutaneous side effects that are usually mild and consist of minor maculopapular rashes, erythema, and petechial lesions, as well as multiple black box warnings associated with severe hypersensitivities [11,16]. Drug-induced angioedema is a rare but demonstrated side effect of carbamazepine administration, which presents as edema that most commonly affects the head and neck region, potentially causing life-threatening airway obstruction [16]. Patients undergoing radiation therapy for head and neck cancer may experience a variety of symptoms including mucositis and ulcers, neuropathic pain, odynophagia, and decreased oral intake [13]. Patients who experience trigeminal pain following radiation are commonly treated with Carbamazepine. In this case report, we discuss a patient who was undergoing concurrent chemoradiation therapy for squamous cell carcinoma of the oropharynx who presented with angioedema likely secondary to carbamazepine use for trigeminal pain, versus radiation-induced edema and mucositis.

## Case

- 88 yo male presented to the ED with acute onset of muffled voice, throat and tongue swelling, difficulty swallowing secretions, and difficulty breathing within several hours after taking one dose of 100 mg carbamazepine.
- Medical history was significant for Stage III squamous cell carcinoma of the left base of tongue, and he was undergoing concurrent CRT. The patient also had a tooth extraction performed on a left lower tooth prior to beginning RT. The patient had received a total of 26 Gy of radiation treatments (13 fractions) thus far in his RT; however, needed a prolong break due to having significant pain originally thought to be related to mucositis and thrush (treated with mouthwash containing nystatin, hydrocortisone, and diphenhydramine, along with a lidocaine solution, diflucan, and hydrocodone).
- During an on treatment visit he characterized pain consistent with trigeminal neuralgia. The patient was started on 100 mg carbamazepine BID. Several hours after the patient's first dose of carbamazepine, he began to have a muffled voice and was taken to the local ED. Upon initial evaluation, the patient was hemodynamically stable and had 100% oxygen saturation on room air; however, he had increased difficulty swallowing secretions, muffled voice, and obvious swelling of the lower face, floor of the oropharynx, and throat. Of note, the patient had allergies to penicillin and piperacillin-tazobactam (unknown reaction) and was not on any known ACE-inhibitors. Ddx included carbamazepine-induced angioedema, Ludwigs angina, and radiation-induced mucositis and swelling.
- The patient was given epinephrine, methylprednisolone 125 mg, and diphenhydramine 25 mg while in the ED. A neck CT scan on admission showed diffuse edema throughout the oropharynx, mouth floor, and tongue base as well as myositis throughout the floor of mouth musculature without abscess formation (Figure 1). The patient's symptoms had not improved on reevaluation and the patient was intubated to prevent further deterioration. He was treated with dexamethasone 4 mg IV q6hrs.
- The patient was subsequently found to have Streptococcus salivarius bacteremia in 1 out of 2 blood culture bottles, and he was treated with IV cefepime and metronidazole. The bacteremia was suspected to be related to mouth flora from a tooth extraction one month prior to his admission.
- On a repeat neck CT on day 4 of admission (Figure 2), the patient had no obvious improvement in his swelling and may have even had minimal progression of his mouth floor, base of tongue, and oropharynx edema. Radiology felt that the patient's imaging findings were consistent with recent radiation treatment but could not exclude infection.
- The patient stayed intubated in the ICU for 5 days and had slow continuous improvement in his symptoms. The patient was discharged on day 10 with an oral dexamethasone taper x 15 days, and IV Ceftriaxone 2g daily x 14 days. He was also instructed to discontinue carbamazepine. Further radiation was delayed due to his current acute medical issues.

## Imaging



Figure 1: CT with contrast of the head and neck on day 1 of admission. (6 days after last radiation treatment), revealing (A) extensive subglottic edema and swelling, (B) subcutaneous fat stranding in anterior neck tissues, and (C) myositis and diffuse edema of the oropharynx and base of tongue.

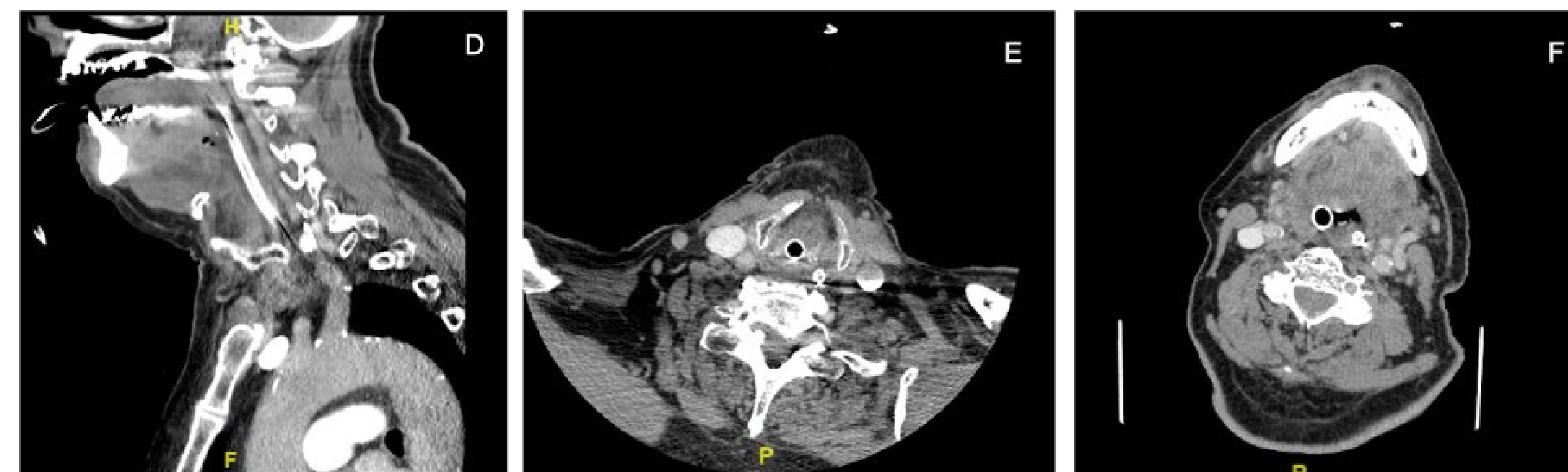


Figure 2: Images from the follow-up CT scan with contrast of the head and neck on day 4 of admission, revealing (D) re-demonstrated subglottic edema and swelling, (E) re-demonstrated subcutaneous fat stranding in anterior neck tissues, and (F) progression of myositis and diffuse edema of the oropharynx and mouth floor musculature.

## References

- Elias A, Madhusoodanan S, Pudukkadan D, Antony JT. Angioedema and maculopapular eruptions associated with carbamazepine administration. *CNS Spectr*. 2006; 11(5): 352-354. <https://www.ncbi.nlm.nih.gov/pubmed/16641839>. doi:10.1017/s1092852900014474.
- Frickle-Galindo I, LLarena A, Jung-Cook H, López-López M. Carbamazepine adverse drug reactions. *Expert Rev Clin Pharmacol*. 2018; 11(7): 705-718. <https://www.ncbi.nlm.nih.gov/pubmed/29898616>. doi:10.1080/17512433.2018.1486707.
- Giatakis A, I. Pototschnig, C. Use of erbium laser in the treatment of persistent post-radiation laryngeal edema: a case report and review of the literature. *World J Surg Onc* 16, 176 (2018). <https://doi.org/10.1186/s12957-018-1480-9>
- Glastonbury CM, Parker EE, Hoang JK. The Postirradiation Neck: Evaluating Response to Treatment and Recognizing Complications. *American Journal of Roentgenology*. 2010; 195(2). doi:10.2214/ajr.09.4122.
- Gronseth G, Cruccu G, Alksne J, Argoff C, Brainin M, Burchiel K, et al. Practice parameter: the diagnostic evaluation and treatment of trigeminal neuralgia (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology and the European Federation of Neurological Societies. *Neurology*. 2008; 71(15): 1183-1190. <https://www.ncbi.nlm.nih.gov/pubmed/18716236>. doi:10.1212/01.wnl.0000326598.83183.04.
- Gupta SN, Gupta VS. Angioedema Caused by Carbamazepine or Acetazolamide: A Single Drug Solution - An Illustrative Case Report. *Neuro Open J*. 2014; 1(1): 20-22. <https://doi.org/10.17140/NOJ-1-105>. doi:10.17140/NOJ-1-105.
- Inomata N. Recent advances in drug-induced angioedema. *Allergol Int*. 2012; 61(4): 545-557. <https://www.ncbi.nlm.nih.gov/pubmed/23183389>. doi:10.2332/allergolint.12-RAI-0493.
- Ishigami K, Averill SL, Pollard JH, McDonald JM, Sato Y. Radiologic manifestations of angioedema. *Insights Imaging*. 2014;5(3):365-374. doi:10.1007/s13244-014-0329-1
- Maan JS, Duong TvH, Saadabadi A. Carbamazepine. [Updated 2020 Oct 28]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK482455/>
- Maria O, Eliopoulos N, Muanza T. Radiation-Induced Oral Mucositis. *Front Oncol*. 2017; 7: 89. <https://www.ncbi.nlm.nih.gov/pubmed/28589080>. doi:10.3389/fonc.2017.00089.
- Mehta M, Shah J, Khakhkhari T, Shah R, Hemavathi KG. Anticonvulsant hypersensitivity syndrome associated with carbamazepine administration: Case series. *J Pharmacol Pharmacother*. 2014; 5(1): 59-62. <https://www.ncbi.nlm.nih.gov/pubmed/24554914>. doi:10.4103/0976-500X.124428.
- Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther*. 1981; 30(2): 239-245. <https://www.ncbi.nlm.nih.gov/pubmed/7249508>. doi:10.1038/clpt.1981.154.
- Rao D, Behzadi F, Le RT, Dagan R, Fiestler P. Radiation Induced Mucositis: What the Radiologist Needs to Know. *Curr Probl Diagn Radiol*. 2020;. doi:10.1067/j.cpradiol.2020.10.006.
- Ropper AH, Cruccu G, Di Stefano G, Truini A. Trigeminal Neuralgia. *N Engl J Med*. 2020; 383(8): 754-762. <https://www.ncbi.nlm.nih.gov/pubmed/32813951>. doi:10.1056/NEJMra1914484
- Sonis ST. The Pathobiology of Oral Mucositis. In: *Oral Mucositis*. Place of publication: Springer Nature; 2012. : 7-13. doi:10.1007/978-1-907673-46-7\_2.
- Subramanian A, Adhimoalam M, Gopalakrishnan S, Rajamohammed MA. Carbamazepine-induced angioedema. *J Basic Clin Pharm*. 2016 Sep;7(4):120-122. doi:10.4103/0976-0105.189436. PMID: 27999472; PMCID: PMC5153889.
- The use of the WHO-UMC system for standardized case causality assessment. World Health Organization (WHO) - Uppsala Monitoring Centre. Available from: <http://www.who-umc.org/Graphics/24734.pdf> [Last accessed on 2020 Dec 21].

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## Discussion

Carbamazepine is indicated treatment for partial seizures, acute mania, bipolar disorder, and is first-line therapy for trigeminal neuralgia [9]. The most common adverse effects are dizziness, drowsiness, nausea, vomiting, and ataxia [9]. It also has a black box warning for severe dermatologic reactions associated with the HLAB1502 gene including SJS/TEN and aplastic anemia/agranulocytosis [2,9]. Carbamazepine-induced cutaneous adverse reactions occur in approximately 3% of the population and usually consist of mild maculopapular rash, erythema, urticaria, and purpuric petechia [9,11,16]. Although extremely rare, carbamazepine induced angioedema was shown in a few cases upon literature review [1,6,11,16].

Angioedema involves vascular reaction and leakage resulting in deep dermal and subcutaneous non-pitting edema usually in the head and neck. There are multiple mechanisms for drug-induced angioedema including IgE mediated reaction causing mast cell degranulation and histamine release (allergic) and/or bradykinin dependent mechanism resulting in inflammation and damage to blood vessels. In contrast to allergic angioedema, there has been no established effective treatment for drug-related kinin-dependent angioedema although steroids are generally used. NSAIDs and ACE-inhibitors are the most common drugs that cause kinin-dependent angioedema; in these cases, symptoms usually resolve within 72 hours with or without treatment [7]. The most common CT imaging finding of head and neck angioedema on CT is glossomegaly with decreased attenuation. There may also be evidence of face and neck swelling, with subcutaneous fat stranding [8].

Radiation induced oral mucositis (RIOM) is one of the major toxicities of radiation therapy in patients with head and neck cancer and occurs in up to 80% of patients [13]. Although IMRT (intensity-modulated RT) attempts to reduce radiation dose to healthy tissues, oral mucosa is often in the path of radiation and mucosal cells are highly susceptible to RT induced damage. RIOM occurs in stages as a result of normal tissue injury and healing and can range in severity from mild irritation and pain to the complete inability to tolerate oral intake and even sepsis from loss of protective epithelial borders [10,13]. The first signs of mucositis usually develop approximately two weeks after initiation of RT and typically continue to persist 2-4 weeks after therapy but can take months to fully resolve. Imaging findings of early RT effects can include enhancing mucosa, salivary gland inflammation, retropharyngeal effusion, fat stranding, skin and muscle thickening, hyperemia, and mucosal atrophy [13].

Although airway obstruction caused by carbamazepine induced angioedema is rare, this is favored as the cause of our patient's symptoms as his presentation was very atypical of radiation-induced mucositis or edema as the onset occurred acutely and within hours after medication administration. He had also received a prolonged treatment break from radiation therapy and was on proper medications to help with radiation-induced symptoms. He was very early in his treatment regimen and had only received a total of 26 Gy which, typically, should not cause this patient's level of symptoms. Although RIOM and radiation-induced edema has characteristics that may appear similar on imaging, these are very non-specific. When using the Naranjo algorithm for adverse drug reaction probability as well as the WHO-UMC system of causality, our patient's symptoms fall under "probable" as a result of carbamazepine administration as the reaction followed a reasonable temporal sequence of drug administration, followed a recognized response to the suspected drug, was confirmed by withdrawal (but not re-exposure) to the drug, and could not be reasonably explained by alternative causes [12,17].

## Conclusion

Drug-induced angioedema is a rare but demonstrated side effect of carbamazepine. Physicians and other prescribers should be aware of this side effect and make their patients aware of this and when to seek emergency care. RIOM is also a common side effect of RT in patients with head and neck cancer. Although imaging may show evidence consistent with RIOM, these are non-specific and other mechanisms should also be considered based on patient symptoms.