CASE REPORT

# A Rare Case of High-grade Parotid Carcinoma with Neuroendocrine Differentiation

Tee S Peng[1], Norhafiza M Lazim[2], Kuhan Kanagaratnam[3], Hafiz BM Mahbob[4], Intan N Darwin[5], Jasmi Ramlan[6]

*Received on:* 18 April 2024; *Accepted on:* 01 October 2024; *Published on:* XX XXXX XX

## Abstract

**Aim:** To discuss a rare case of parotid gland poorly differentiated carcinoma with neuroendocrine differentiation.

**Background:** Salivary gland tumor with neuroendocrine differentiation is a rare occurrence and accounts for only 1–3% out of all major salivary gland malignancies. They are most commonly presented with high-grade histomorphology features and warrant an aggressive treatment.

**Case description:** Recently we encountered a 54-year-old patient who presented with left cheek swelling for 6 months which was progressively increasing in size. The patient had an excision biopsy of the mass via intraoral approach performed by another hospital before being referred to our center, which revealed high-grade neuroendocrine carcinoma with metastatic poorly differentiated malignancy from the lung primary. The intraoral examination noted a small swelling over the left buccal region measuring approximately 2 × 2 cm which was firm to hard in consistency. The cranial nerve examination revealed left facial nerve palsy House-Brackman grade IV at all five branches with reduced sensation over the left trigeminal distribution. Positron emission tomography (PET/CT) scan showed focal F-fluorodeoxyglucose (FDG) uptake at the left masseter muscle and no FDG uptake in the lung to suggest primary from the lung. He underwent left total parotidectomy and left supraomohyoid neck dissection in which the final histopathology examination revealed poorly differentiated carcinoma with neuroendocrine differentiation. He was subsequently referred to oncology for postoperative chemoradiotherapy commencement.

**Conclusion:** Prompt definitive diagnosis is of utmost importance to initiate targeted therapy early. Treatments include radical surgical resection with the addition of adjuvant chemotherapy and radiotherapy to reduce the risk of tumor recurrence as well as strict long-term follow-up.

**Clinical significance:** This case underscores the importance of detailed clinical evaluation with combinations of radiological imaging and immunohistochemistry staining in order to differentiate between primary or secondary metastasis of salivary gland neuroendocrine tumor.

**Keywords:** Carcinoma, Case report, Neuroendocrine tumors, Parotid gland, Salivary glands.

*Otorhinolaryngology Clinics: An International Journal* (2024): 10.5005/jp-journals-10003-1538

## Background

Neuroendocrine neoplasm encompasses a diverse spectrum of diseases which can be classified into epithelial or non-epithelial origin, functional status, and anatomical location as well as graded according to the cytomorphology differentiation of the histopathology specimen.[1–3] Although neuroendocrine can be originated from any tissues and organs in the body, its primary tumor usually comes from the gastrointestinal, lung, and tracheobronchial complex.[4,5] The incidence rate of all neuroendocrine tumor is rare with an estimated 1.3–4.5 per 100,000 people per year in the United States and it is even rare in the head and neck region.[4,6] The most common neuroendocrine tumor in the head and neck comes from the larynx even though it only comprises 0.5–1% of all laryngeal neoplasms.[1,7] Regarding the neuroendocrine carcinoma of the salivary gland, it is even rare but well documented in the literature. It can be a primary tumor or metastatic tumor originating from the skin, digestive tract, or lungs. Primary tumor comprises 1–3% of major salivary gland malignancy and it can originate *de novo* or undergo malignant transformation from a relatively benign salivary neoplasm.[8] They commonly belong to high-grade neoplasm as compared to well-differentiated or moderate-differentiated histopathology examination.[7–9]

Neuroendocrine tumors often caused confusion and dilemma among the pathologists to conclude this diagnosis as it was a great mimicker to other pathologies such as medullary cell carcinoma, paraganglioma, Merkel cell carcinoma, melanoma, basaloid squamous cell carcinoma, etc.[8–12]

[1,2]Department of Otorhinolaryngology – Head and Neck Surgery, School of Medical Sciences, Health Campus, Universiti Sains Malaysia, Kubang Kerian, Kelantan, Malaysia

[3,4]Department of Otorhinolaryngology – Head and Neck Surgery, Hospital Sultan Ismail, Jalan Mutiara Emas Utama, Taman Mount Austin, Johor Bahru, Johor, Malaysia

[5,6]Department of Pathology, Hospital Sultanah Aminah, Jalan Persiaran Abu Bakar Sultan, Johor Bahru, Johor, Malaysia

**Corresponding Author:** Norhafiza M Lazim, Department of Otorhinolaryngology – Head and Neck Surgery, School of Medical Sciences, Health Campus, Universiti Sains Malaysia, Kubang Kerian, Kelantan, Malaysia, Phone: +60199442664, e-mail: norhafiza@usm.my

**How to cite this article:** Peng TS, Lazim NM, Kanagaratnam K, *et al*. A Rare Case of High-grade Parotid Carcinoma with Neuroendocrine Differentiation. Int J Otorhinolaryngol Clin 2024;xx(x):xx–xx.

**Source of support:** Nil

**Conflict of interest:** None

**Patient consent statement:** The author(s) have obtained written informed consent from the patient for publication of the case report details and related images.

## Case Description

A 54-year-old Chinese gentleman who had an underlying history of chronic lymphocytic leukemia completed chemotherapy 8 months ago presented with left cheek swelling for 6 months duration.

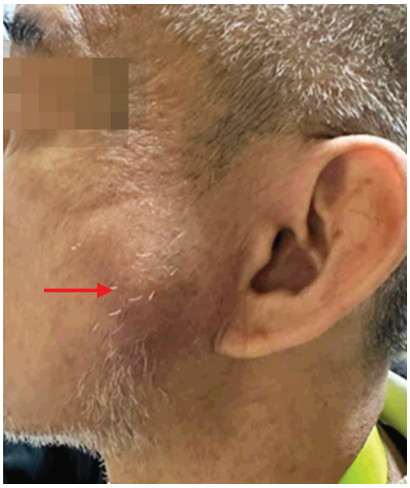


**Fig. 1:** Red arrow pointing at the left parotid mass measuring 4 × 5 cm in the longest axis

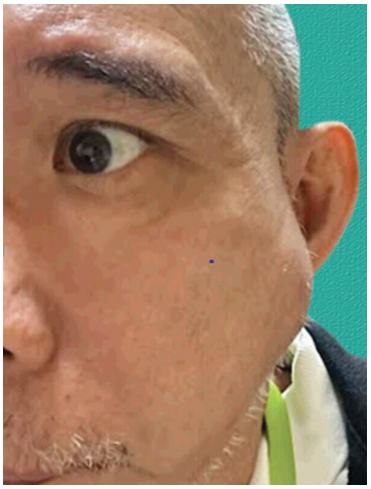


**Fig. 2:** Left facial nerve palsy with House-Brackmann grade IV at all five branches preoperatively

The swelling progressively increased in size and was associated with intermittent pain and numbness over the left face. He had previously sought treatment at another hospital and an excisional biopsy of the left cheek was performed via intraoral approach. Histopathology report reviewed high-grade neuroendocrine carcinoma with metastatic poorly differentiated malignancy from the lung primary. He was subsequently referred to our hospital for continuation of treatment. Clinically the mass measuring 4 × 5 cm over the left preauricular region, firm to hard in consistency, fixed to underlying structure, and no overlying skin changes (Fig. 1).

Intraorally, there was a small swelling over the left buccal region measuring about 2 × 2 cm, firm to hard in consistency, without breaching the overlying mucosa and there was no extension of mass to the gingiva or retromolar trigone. The cranial nerve examination revealed left facial nerve palsy House-Brackman grade IV at all five branches and reduced sensation over the left trigeminal distribution (Fig. 2). Otherwise, he had no palpable cervical lymph nodes and no significant findings from the otoscopy, rhinoscopy as well as laryngoscopy. Computed tomography (CT) scan of the neck revealed left parotid mass measuring 4.5 × 2.6 × 4.2 cm (anteroposterior × width × craniocaudal) in dimension abutting

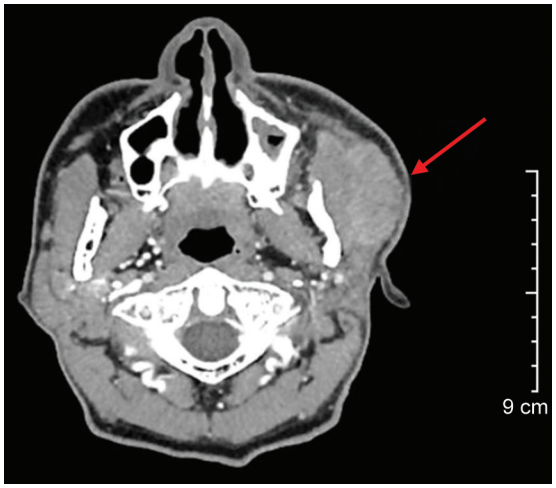



**Fig. 3:** Computed imaging showing the left parotid mass (red arrow) measuring 4.5 × 2.6 × 4.2 cm (anteroposterior × width × craniocaudal) in dimension abutting the left masseter

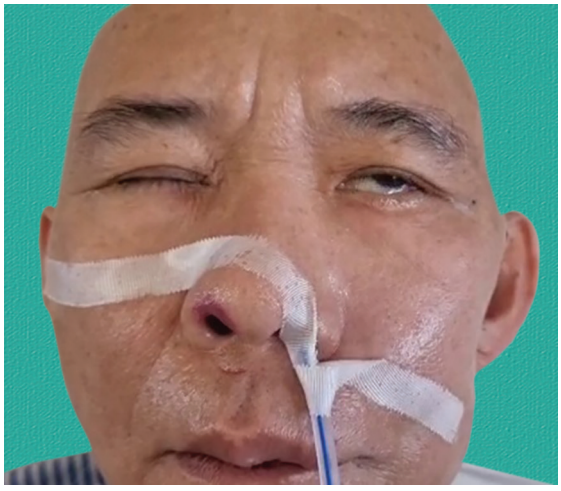
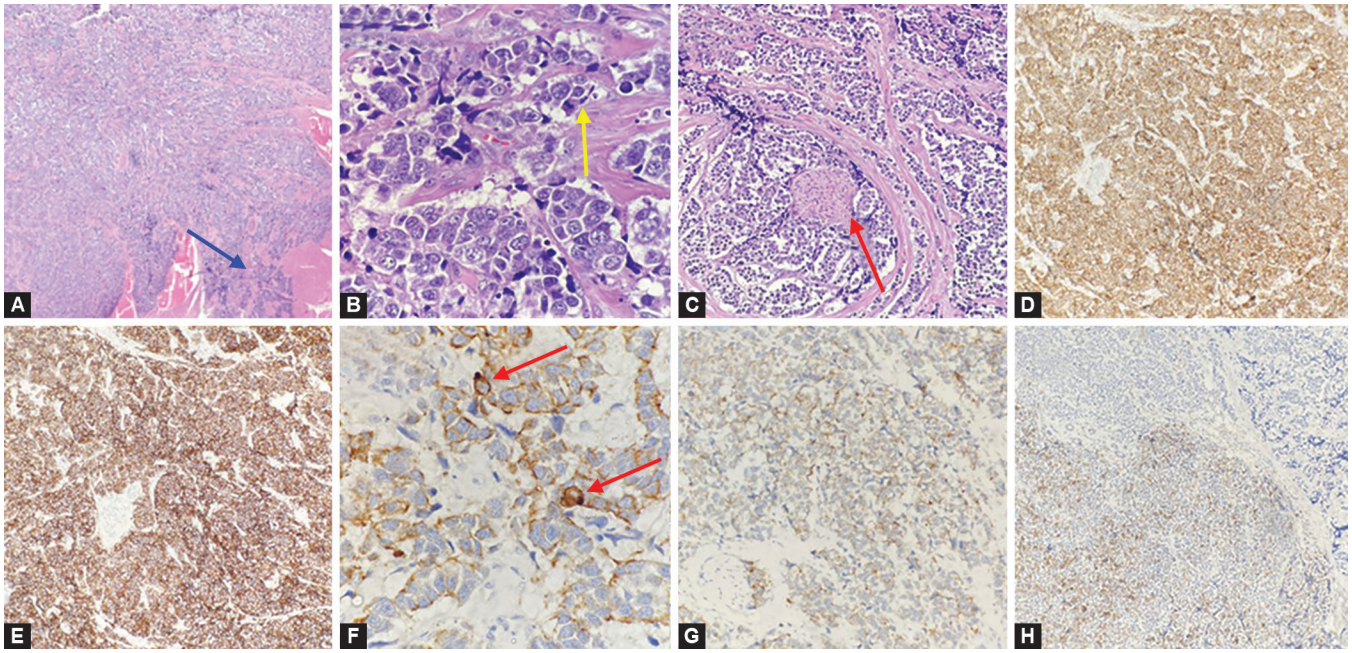


**Fig. 4:** Left facial nerve palsy with House-Brackmann grade IV at all 5 branches postoperatively

the left masseter muscle (Fig. 3). Positron emission tomography (PET/CT) scan showed focal F-fluorodeoxyglucose (FDG) uptake at the left masseter muscle (standardized uptake value 11.3). There was no enlarged node at the cervical region and no FDG uptake in the lung to suggest primary from the lung. The second review of the left buccal mass specimen done by our regional pathologist favored high-grade poorly differentiated carcinoma with neuroendocrine differentiation but was unable to give a conclusive diagnosis due to the extensively crushed sample. A multidisciplinary conference was conducted and was planned for left total parotidectomy with left supraomohyoid neck dissection. Intraoperatively, noted the parotid mass measuring 4 × 4 cm, firm in consistency overlying the left masseter muscle extending toward part of the left superficial lobe of the parotid gland. The buccal branch of the facial nerve pierced through the tumor and was sacrificed during the dissection. Postoperatively, the patient's left facial nerve deteriorated to House-Brackmann grade IV over all five branches (Fig. 4). Otherwise, there were no other major complications from the surgery and the surgical wound healed well. The final histopathology diagnosis concluded left parotid




**Figs 5A to H:** (A) Microscopic examination revealed malignant cells arranged in prominent organoid, and nest-like pattern with evidence of adjacent skeletal muscle invasion as shown by blue arrow [hematoxylin-eosin (H&E) stained, original magnification ×100]; (B) These cells exhibit mild to moderately pleomorphic, hyperchromatic nuclei, and scanty cytoplasm with brisk mitosis as shown by yellow arrow (H&E stained, original magnification ×600); (C) There was evidence of perineural invasion as shown by red arrow (H&E stained, original magnification ×200); (D) IHC stained with CD117 manifested significant immunoreactivity (original magnification x100); (E) IHC stained with BER-EP4 demonstrated diffusely positivity (original magnification ×100); (F) IHC with CKAE1/AE3 stained were focally positive as shown by red arrow (paranuclear-dot) [original magnification ×600]; (G) Immunohistochemistry stained with CK7 showed weakly positive (original magnification ×200); and (H) These tumor cells expressed immunoreactivity with CD56 stained confirming a neuroendocrine differentiation (original magnification ×100)

poorly differentiated carcinoma with focal neuroendocrine differentiation after exclusion of metastasis or another primary tumor. Immunohistochemistry (IHC) stained with BEREP4 and CD117 showed diffusely positive whereas pan-cytokeratin AE1/AE3 stained revealed focally positive with paranuclear-dot. Other stains that were shown to be weakly positive were CK7, CK5/6, EMA, GATA3, and CD56 (Fig. 5). Neuroendocrine markers stained such as CK 20, CD99, s100, vimentin, synaptophysin, and chromogranin were negative. The Ki-67 protein and proliferative index was about 70%. As for the safe margin of the tumor, it was less than 1 mm from the superior, inferior, medial, lateral, and anterior surgical margins. There was evidence of perineural, lymphovascular, and adjacent muscle invasion from the tumor specimen. Otherwise, the supraomohyoid lymph node was free from tumor metastasis (0/7). Postoperatively, this patient was started on combined chemoradiotherapy and thus far has been tolerating well without any major complications.

## Discussion

From the case presented here, this patient has metachronous left parotid malignancy with an interval of 8 months after he completed chemotherapy for his chronic lymphocytic leukemia. Based on the literature search, there was no direct association between chronic lymphocytic leukemia and neuroendocrine tumor.[13] However, this might be due to the patient's immunodeficiency status induced by the leukemia as well as the chemotherapy.[8]

Neuroendocrine tumor in the head and neck area was a rare occurrence with the salivary gland being the second most common anatomical site after the larynx.[14–16] Salivary gland neuroendocrine neoplasm (NEN) represents less than 1% of all salivary gland neoplasm and was estimated around 2% of salivary gland malignancy.[10] Among these, the parotid gland is the most common site reported followed by the submandibular gland, sublingual gland, and minor salivary glands.[8,10] Although previous literature narrates the incidence of parotid neuroendocrine tumor, it is worth highlighting salivary gland neuroendocrine tumor as one of the important differential diagnoses.

In regard to the latest classification by WHO in 2022 for the epithelial neuroendocrine neoplasm of the salivary gland, a well-differentiated neuroendocrine tumor can be subdivided into G1, G2, and G3 based on the evidence of necrosis and rate of mitosis. Poorly differentiated neuroendocrine carcinoma is further subdivided into small cell carcinoma and large cell carcinoma based on the cytomorphology of the tumor specimen with more than 10 mitoses per 2 $mm^2$ and Ki67 proliferative index of more than 20%.[15] Poor differentiation of tumor cells is considered as a high grade which carries a poor prognosis, whereas well differentiation of a tumor specimen is classified as low grade and associated with a good prognosis.[15] In comparison, previous case series found that the tumor cell type did not correlate to the prognosis but factors such as tumor size larger than 3 cm in diameter, CK20 negativity, and lesser number of positive neuroendocrine markers by IHC carrier a poorer prognosis.[10,12] According to Pohar et al., age more than 55 years old and advanced tumor stage was associated with a significant poorer 5-year survival rate.[17]

Even though the prognosis of parotid neuroendocrine tumor was reported better than the larynx and lung, it should be treated aggressively due to its high risk of local recurrence and metastases in >50% of cases.[10,12,18,19] In our case reported here, the patient has all the poor prognostic factors mentioned above such as the tumor

size being larger than 3 cm with surgical margin <1 mm, CK20 negativity, most of the neuroendocrine markers were negative and the WHO classification of poorly differentiated carcinoma with Ki 67 proliferative index >70%. Hence, this patient warranted an aggressive targeted therapy which included total parotidectomy and supra-omohyoid neck dissection.

Before the commencement of treatment for salivary gland neuroendocrine carcinoma, it is important to look for the possibility of metastasis from the other primary organs specifically from the lung with great emphasis on the detailed clinical evaluation and imaging study solely based on the histopathology alone is insufficient to distinguish between primary or secondary tumor.[10,20,21] Until today, there is still no established staging system and no consensus on the best treatment option for salivary gland neuroendocrine carcinoma.[5,9] Most of the authors advocated radical tumor resection and elective neck dissection with the addition of postoperative chemoradiotherapy if there is a high risk for tumor recurrence.[5,10,18,21] Pohar et al. proved that surgery with adjuvant radiotherapy significantly improved locoregional control compared to the surgery-only group even though it did not improve the overall survival rate.[17] Furthermore, a single modality of radiotherapy was feasible for those patients not suitable for surgery but with the condition of strict long-term follow-up.[10]

In conclusion, timely diagnostic evaluation with appropriate investigation is of utmost importance to initiate targeted therapy early for salivary gland neuroendocrine carcinoma. Despite that there is still no consensus on the best treatment for salivary gland neuroendocrine tumors, current treatments including radical surgical resection with the addition of adjuvant chemotherapy and radiotherapy are deemed to be adequate to reduce the risk of tumor recurrence as well as strict regular follow-up. The scarcity of salivary gland neuroendocrine carcinoma warrants more future research with a larger sample size analysis to offer the best therapeutic options as well as prolong the survival rate for the patients.

## Clinical Significance

This case underscores the importance of detailed clinical evaluation with the combination of radiological imaging and IHC staining to differentiate between primary and secondary metastasis of neuroendocrine tumors. This is because the incidence of primary salivary gland neuroendocrine tumor is rare, to begin with, and solely based on histopathology examination can mislead the treating surgeon to be a secondary metastasis.

## Orcid

*Tee S Peng* https://orcid.org/0009-0004-4034-4374
*Norhafiza M Lazim* https://orcid.org/0000-0002-2367-1814
*Kuhan Kanagaratnam* https://orcid.org/0009-0002-4336-4771
*Hafiz BM Mahbob* https://orcid.org/0000-0002-5650-6954

## References

1. Ferlito A, Devaney KO, Rinaldo A. Neuroendocrine neoplasms of the larynx: Advances in identification, understanding, and management. Oral Oncol 2006;42(8):770–788. DOI: 10.1016/J.ORALONCOLOGY.2006.01.002.
2. Helderman NC, Suerink M, Kilinç G, et al. Relation between WHO classification and location-and functionality-based classifications of neuroendocrine neoplasms of the digestive tract. Neuroendocrinol 2024;114(2):120–133. DOI: 10.1159/000534035.
3. Rindi G, Klimstra DS, Abedi-Ardekani B, et al. A common classification framework for neuroendocrine neoplasms: An International Agency for Research on Cancer (IARC) and World Health Organization (WHO) expert consensus proposal. Mod Pathol 2018;31(12):1770–1786. DOI: 10.1038/S41379-018-0110-Y.
4. Hemminki K, Li X. Incidence trends and risk factors of carcinoid tumors: A nationwide epidemiologic study from Sweden. Cancer 2001;92(8):2204–2210. DOI: 10.1002/1097-0142(20011015)92:8<2204::AID-CNCR1564>3.0.CO;2-R.
5. Mascitti M, Luconi E, Togni L, et al. Large cell neuroendocrine carcinoma of the submandibular gland: A case report and literature review. Pathologica-J Ital Soc Anat Pathol Diagn Cytopathol 2019;111(2):70–75. DOI: 10.32074/1591-951X-13-19.
6. Modlin IM, Lye KD, Kidd M. A 5-decade analysis of 13,715 carcinoid tumors. Cancer 2003;97(4):934–959. DOI: 10.1002/CNCR.11105.
7. Martínez-Sáez O, Molina-Cerrillo J, Moreno García del Real C, et al. Primary neuroendocrine tumor of the parotid gland: A case report and a comprehensive review of a rare entity. Case Rep Otolaryngol 2016. DOI: 10.1155/2016/6971491.
8. Chernock RD, Duncavage EJ. Proceedings of the NASHNP Companion Meeting, March 18th, 2018, Vancouver, BC, Canada: Salivary neuroendocrine carcinoma—an overview of a rare disease with an emphasis on determining tumor origin. Head Neck Pathol 2018;12:13–21. DOI: 10.1007/S12105-018-0896-4.
9. Said-Al-Naief N, Sciandra K, Gnepp DR. Moderately differentiated neuroendocrine carcinoma (atypical carcinoid) of the parotid gland: Report of three cases with contemporary review of salivary neuroendocrine carcinomas. Head Neck Pathol 2013:295–303. DOI: 10.1007/S12105-013-0431-6.
10. Jorcano S, Casado A, Berenguer J, et al. Primary neuroendocrine small cell undifferentiated carcinoma of the parotid gland. Clin Transl Oncol 2008;10:303–306. DOI: 10.1007/S12094-008-0203-Z.
11. Kao HL, Chang WC, Li WY, et al. Head and neck large cell neuroendocrine carcinoma should be separated from atypical carcinoid on the basis of different clinical features, overall survival, and pathogenesis. Am J Surg Pathol 2012;36(2):185–192. DOI: 10.1097/PAS.0B013E318236D822.
12. Nagao T, Gaffey TA, Olsen KD, et al. Small cell carcinoma of the major salivary glands: Clinicopathologic study with emphasis on cytokeratin 20 immunoreactivity and clinical outcome. Am J Surg Pathol 2004;28(6):762–770. DOI: 10.1097/01.PAS.0000126776.65815.48.
13. Russo F, Guadagni S, Corazzelli G, et al. Chronic lymphocytic leukaemia and neuroendocrine cancer. Br J Haematol 1999;105(4):989–992. DOI: 10.1046/J.1365-2141.1999.01472.X.
14. Ferlito A, Silver CE, Bradford CR, et al. Neuroendocrine neoplasms of the larynx: An overview. Head & Neck: Head Neck-J Sci Spec 2009;31(12):1634–1646. DOI: 10.1002/HED.21162.
15. Mete O, Wenig BM. Update from the 5th edition of the World Health Organization Classification of head and neck tumors: Overview of the 2022 WHO Classification of head and neck neuroendocrine neoplasms. Head Neck Pathol 2022;16(1):123–142. DOI: 10.1007/s12105-022-01435-8.
16. Mills SE. Neuroectodermal neoplasms of the head and neck with emphasis on neuroendocrine carcinomas. Mod Pathol 2002;15(3):264–278. DOI: 10.1038/MODPATHOL.3880522.
17. Pohar S, Gay H, Rosenbaum P, et al. Malignant parotid tumors: Presentation, clinical/pathologic prognostic factors, and treatment outcomes. Int J Radiat Oncol Biol Phys 2005;61(1):112–118. DOI: 10.1016/J.IJROBP.2004.04.052.
18. Lin YC, Wu HP, Tzeng JE. Small-cell undifferentiated carcinoma of the submandibular gland: An extremely rare extrapulmonary site. Am J Otolaryngol 2005;26(1):60–63. DOI: 10.1016/J.AMJOTO.2004.06.013.
19. Liu M, Zhong M, Sun C. Primary neuroendocrine small cell carcinoma of the parotid gland: A case report and review of the literature. Oncol Lett 2014;8(3):1275–1278. DOI: 10.3892/OL.2014.2258.
20. Casas P, Bernáldez R, Patrón M, et al. Large cell neuroendocrine carcinoma of the parotid gland: Case report and literature review. Auris Nasus Larynx 2005;32(1):89–93. DOI: 10.1016/J.ANL.2004.11.016.
21. Yamamoto N, Minami S, Kidoguchi M, et al. Large cell neuroendocrine carcinoma of the submandibular gland: Case report and literature review. Auris Nasus Larynx 2014;41(1):105–108. DOI: 10.1016/J.ANL.2013.07.010.