Avicenna J Dent Res. 2017 September; 9(3):e33366. doi: 10.5812/ajdr.33366.

Published online 2016 July 4. **Case Report**

Small Cell Neuroendocrine Carcinoma of the Salivary Glands of the Palate: Report of a Rare Case and a Review of the Literature

Parviz Deyhimi,[1] Mohammad Razavi,[1] Ali Tavakolli Hoseini,[2] and Batoul Alishahi[3,*]

[1]Oral and Maxillofacial Pathology Department, Dentistry School, Isfahan University of Medical Sciences, Isfahan, IR Iran
[2]Oral and Maxillofacial Pathology Department, Dentistry School, Shahid Saddoughi University of Medical Sciences, Yazd , IR Iran
[3]Oral and Maxillofacial Pathologist, Razi Herbal Medicines Research Center, Dental School of Khorramabad, Lorestan University of Medical Sciences, Khorramabad, Iran

[*]*Corresponding author*: Batoul Alishahi, Oral and Maxillofacial Pathologist, Razi Herbal Medicines Research Center, Dental School of Khorramabad, Lorestan University of Medical Sciences, Khorramabad, Iran. Tel: +98-9131941448, E-mail: Ba.Alishahi@yahoo.com

Received 2015 September 23; **Revised** 2016 January 11; **Accepted** 2016 February 01.

Abstract

Introduction: Small cell neuroendocrine carcinomas (SmCCs) of the salivary glands are rare high grade malignant neoplasms, and the identification of these lesions is often difficult. Histopathological features alone are not sufficient for the diagnosis of SmCCs, and immunohistochemical (IHC) staining is almost always mandatory for confirming the diagnosis.
Case Presentation: We report one salivary SmCC case in a female who presented with swelling on the left side of the face. For a distinct diagnosis, histopathological and IHC evaluation was performed.
Conclusions: The presentation of these cases can be helpful for the histopathological differential diagnosis of similar tumors

Keywords: Case Report, Small Cell Carcinoma, Neuroendocrine, Salivary Glands

1. Introduction

Small cell neuroendocrine carcinomas (SmCCs) are malignant epithelial neoplasms that mostly occur in the lungs (1, 2). Primary extrapulmonary small cell carcinomas (PESmCCs) are a rare malignancy accounting for 2.5% to 5% of all SmCCs. In the head and the neck, SmCCs often arise in the larynx, nasal cavity, paranasal sinuses, pharynx, oral cavity, cervical esophagus, and salivary glands (2, 3). SmCCs in the salivary glands are rare, comprising only 2% of all tumors that occur in the salivary glands (4).

In SmCCs, the atypical cells are almost 2 times larger than the normal small lymphocytes. They are round or oval, and are arranged in solid sheets and nest patterns (5). Therefore, the differential diagnosis of SmCC should include metastatic small cell lung carcinoma, Merkel cell carcinoma, metastatic melanoma, lymphoma, poorly differentiated carcinoma, and other small round cell tumors (3).

SmCC cells react with common neuroendocrine markers such as neuron specific enolase (NSE), neurofilament, synaptophysin, and chromogranin. Additionally SmCC cells may express general epithelial markers such as keratin (3, 6).

SmCCs in salivary glands have a more favorable prognosis than small cell carcinoma in other organs such as the lung, larynx, esophagus, and trachea, with an estimated survival rate after two and five years at 70% and 46%, respectively (2, 7). However, because of the aggressive nature of SmCCs and the frequent occurrence of distant metastasis and recurrence, quick diagnosis of these tumors is important. Accordingly, the definitive diagnosis is made by immunohistochemical (IHC) analysis. Currently the treatment modalities include a combination of surgery, radiotherapy, and chemotherapy (8, 9).

In the current study, the clinical, histopathological and immunohistochemical features of a rare case of SmCC in the minor salivary glands of the palate are discussed.

2. Case Presentation

A 21-year-old female was referred to the department of oral and maxillofacial pathology at Isfahan University of Medical Sciences due to swelling on the left side of the face and on the left side of the nasolabial fold (Figure 1). In intraoral examination, a mass on the left side of the maxilla was observed as involving both the alveolar mucosa and the palate from tooth no. 7 to 15 (Figure 2). Tooth no. 8 and 9 were completely loose. The patient had a history of unexplained tears dropping from the left eye. There was no paresthesia or anesthesia, and the mucosa was normal. This swelling had been progressively in-

creasing and rapidly growing over the course of only six months. A panoramic radiographic image showed a mixed radiolucent-radiopaque lesion from the mesial of the right first molar to the distal of the left second molar (Figure 3). The CT scan revealed a soft tissue mass in the anterior of the maxilla with expansion into the left nasal cavity and the maxillary sinus (of both the axial and coronal plates) (Figure 4).

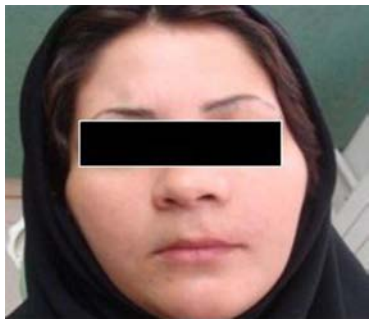

Figure 1. Clinical Appearance of the Patient, Showing Swelling in the Left Side of the Face

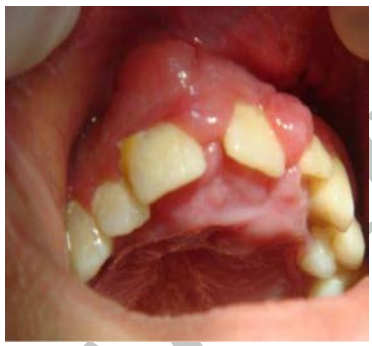

Figure 2. Clinical Appearance of the Tumor in the Left Side of the Maxilla

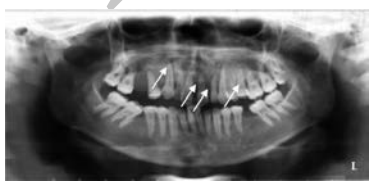

Figure 3. Panoramic View of a Mixed Radiolucent-Radiopaque Lesion from the Mesial of the Right First Molar to the Distal of the Left Second Molar

An incisional biopsy was performed and, based on histopathological consideration, nests and sheets of small round cells with round to oval nuclei, and scant eosinophilic cytoplasm very similar to lymphoma, small cell carcinoma of lung, or any small round cell tumor were observed. Pleomorphism, atypism, hyperchromatism, and mitotic figures were visible to variable degrees (Figure 5A: magnification: ×100; Figure 5B: magnification: ×400).

For a distinct diagnosis, the IHC method was used with markers of leukocyte common antigen (LCA), CD99, vimentin, neuron specific enolase (NSE), desmin, cytokeratins (CKs), and epithelial membrane antigen (EMA). The IHC study demonstrated that the tumor cells did not stain for LCA, CD99, vimentin, or desmin, but these cells were strongly stained positive (4+) for one of the common neuroendocrine markers like NSE, and focally positive (1+) for CKs and EMA. The staining intensity was evaluated with rankings of 0 = negative, +1 = poor, +2 = moderate, +3 = moderate to high, and +4 = very high. These features of the tumor cells were suggestive of small cell neuroendocrine carcinoma.

The patient was treated with a complete resection of the maxilla (total maxillectomy). A gross mass of 6 × 5 × 4 cm3 of the maxilla bulk from tooth no. 5 to 16 was obtained. The margins of the mass were well defined, unencapsulated, and markedly invasive, especially on the palate. The texture of the section was solid and the color was yellow-tan to brown.

Under a light microscope (Olympus BX41), the tumor cells appeared to be round to oval with scattered polygonal cells, prominent nuclei, inconspicuous nucleoli, and scanty cytoplasm. The tumor cells were arranged in solid nests and alveolar patterns. For further study, the IHC method was used to determine the presence of pan-cytokeratin (pan-CK), EMA, CK20, NSE, chromogranin, synaptophysin, S100, and Ki-67.

The following results were obtained: pan-CK and EMA were focally positive (1+), chromogranin was moderately positive (2+), and synaptophysin and NSE were strongly positive (4+). However, the tumor cells did not express CK20 or S100 (Figure 6A, B, C, D ; magnification: ×400).

Because of the involvement of the cervical lymph nodes, neck dissection was performed and microscopically, the same features of the lesion biopsy were viewed with more polygonal cells. The tumor cells were involved in two lymph nodes.

Overall, by considering the medical history, CT scan results, histopathological findings, and IHC analysis, the final diagnosis of small cell neuroendocrine carcinoma with probable origin from the minor salivary glands of the plate was obtained. The patient was followed-up on one month after surgery, and chemotherapy was added to the treatment protocol.

However despite the follow-up and continuing treatment, the patient died one year after surgery because of a

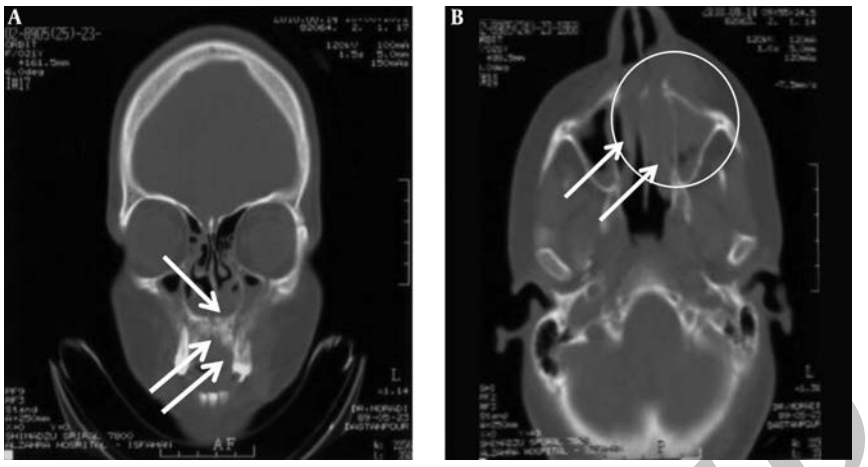

Figure 4. CT Scan Views of a Soft Tissue Mass in the Anterior of the Maxilla with Expansion Into the Left Nasal Cavity and Maxillary Sinus in the Cronal, A and Axial, B View

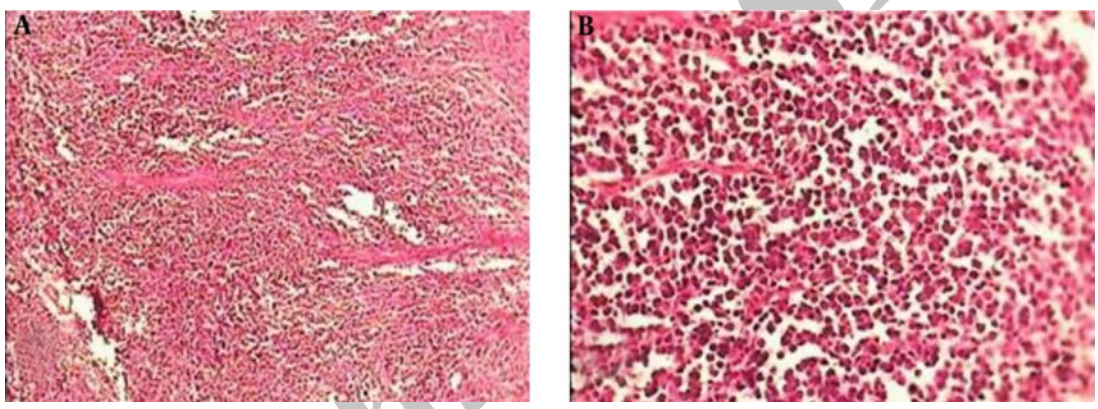

Figure 5. Histopathological Views of Small Cell Carcinoma (Hematoxylin and Eosin Stain), Showing Small Pleomorphic Round or Ovoid Cells Arranged in Solid Nests (A: ×100 Magnification, B: ×400 Magnification)

recurrent tumor and distant metastasis to the liver.

3. Discussion

Small cell neuroendocrine carcinoma (SmCC) is a high grade malignancy that was first observed in the lung (1, 2, 5). SmCC has also been referred to as oat cell carcinoma, poorly differentiated neuroendocrine carcinoma, small cell undifferentiated carcinoma, or anaplastic cell carcinoma (2, 5). SmCC may also occur in non-pulmonary organs in which it is classified as extra-pulmonary small cell carcinoma (EPSmCCs). EPSmCCs can involve different organs such as the head and neck, gastrointestinal tract, genitourinary, and gynecologic organs.

The larynx, nasal cavity, paranasal sinuses, pharynx, oral cavity, cervical esophagus, and salivary glands are most commonly involved in cases involving the head and neck (2, 3). In 1972, Olofsson and Van Nostrand reported the first case of SmCC in the head and neck, specifically located in the larynx (10). SmCCs in the salivary glands are rare and account for approximately 2% of all salivary gland malignancies. Salivary SmCC include 2.8 %and 1.85 % of all major and minor salivary gland tumors, respectively (5). The most common site of involvement of the major salivary glands is the parotid (1, 2).

Extrapulmonary SmCCs including those of the salivary glands behave aggressively much like SmCCs in the lung, and with similar histologic, ultrastructural, and IHC features, but salivary gland SmCCs have a better prognosis in comparison with pulmonary SmCCs (3, 7). Clinically, patients present with a painless, rapidly growing mass that develops in the range of 3 - 6 months (typically less than 3

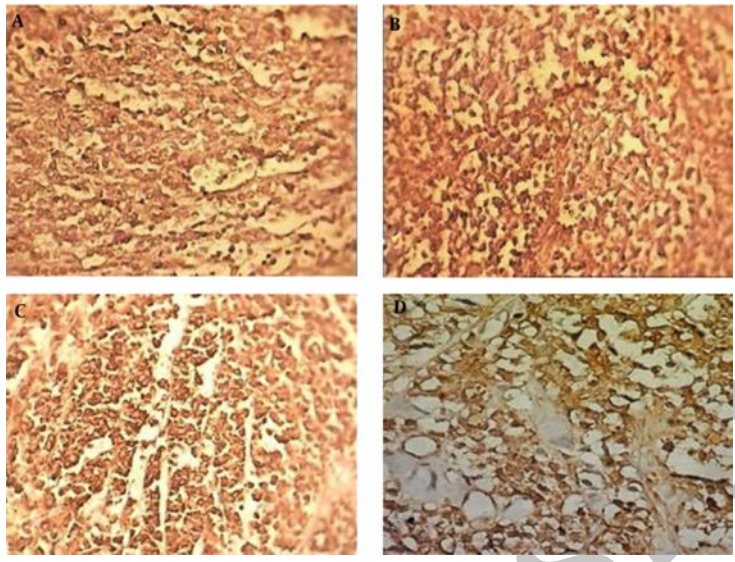

Figure 6. Immunohistochemical Staining for A, Chromogranin (Relatively Positive). B, Cytokeratin (Focally Positive). C, Synaptophysin (Strongly Positive), and D, NSE(Strongly Positive) [×400 Magnification]

months). The tumors are usually found in patients 50 - 70 years of age and more frequently in males (1, 2, 7).

Histologically, these aggressive high grade neoplasms consist of nest, sheet, or ribbon patterns of round, oval, or even fusiform cells measuring as large as or about two times larger than normal small lymphocytes. The cells are typically identified by ill-defined borders, sparse eosinophilic cytoplasm, and pyknotic nuclei, with fine evenly-dispersed clumped chromatin. Nuclear molding and crush artifact may also be observed in these cases, and the nucleoli are inconspicuous (3, 5).

SmCCs have a high mitotic index (averaging 10 mitotic figures per 10 high-power fields) (5). Ductal and squamous differentiation as well as the coexistence of squamous and small cell carcinomas may also be observed (5, 11). Areas of necrosis in these tumors may be visible as well (3, 11). Additionally, vascular and perineural invasion is frequent in the findings (5).

The immunophenotypes of SmCCs reveal both epithelial and primitive neuroendocrine differentiation (3). Immunohistochemically, the tumor cells exhibit positivity for broad-spectrum cytokeratins as seen in punctate parinuclear dot staining. Some SmCCs also stain with cytokeratins 7 and 20 (12). These tumors express one or more neuroendocrine markers that include chromogranin, synaptophysin, and CD56 or the neural cell adhesion molecule (NCAM). Most of tumors also stain positively for EMA and NSE. SmCC may also react with neurofilaments and CD57 (Leu-7) (9, 13).

In their study, Huntrakoon et al. demonstrated that membrane-bound, dense-core neurosecretory granules were observed in ~20% of cases of SmCC of the salivary glands (14). In a study by Eversole and Knapp, 47% of SmCC tumors contained neuroendocrine granules (15). In the present case, the expression of CK and EMA was focally positive, NSE and synaptophysin was strongly positive, and chromogranin was relatively positive, which confirmed the diagnosis of SmCC.

Synaptophysin, a membrane glycoprotein found in small presynaptic vesicles, is one of the neuroendocrine markers that can stain nerve and epithelial tumors (2, 7). Chromogranin is a component of normal chromaffin granules that is frequently seen in many endocrine cells and endocrine tumors. However, this marker is also occasionally expressed in some of the non-neuroendocrine carcinomas and sarcomas (7). NSE is a specific marker for neurons, neuroendocrine cells, and their tumors (5, 7). In some studies, TTF-1 and CD117 are used for the diagnosis of lung SmCC (2). TTF-1 is stained in the epithelial cells of the thyroid glands and lungs and also in the majority of lung. SmCCs and atypical neuroendocrine tumors immunohistochemically react to TTF-1 (2, 3, 16). CD117 is also commonly expressed in gastrointestinal stromal tumors (2, 17). If a tumor is positive for at least one of these neuroendocrine cell markers, then diagnosis of SmCC can be confirmed (2).

The differential diagnosis of salivary SmCC should include an examination for metastatic SmCC of the lung, other types of neuroendocrine or carcinoid tumors,

Merkel cell carcinoma, metastatic melanoma, lymphoma, and poorly differentiated carcinoma. Carcinoid tumors can be easily differentiated from SmCC due to the distinct histopathological features. Merkel cell carcinoma is morphologically similar to salivary SmCC. In addition, both tumors are expressed by CK20 paranuclearly, but these tumors, unlike pulmonary SmCC, are not expressed by TTF-1. Melanoma and lymphoma should be immunohistochemically identified by their specific markers, including S-100, HMB-45, LCA, and CD45. Other differential diagnoses include small round cell tumors such as rhambdomyosarcoma, Ewing's sarcoma, mesenchymal chondrosarcoma, olfractory neuroblastoma, and small cell osteosarcoma that could be differentiated immunophenotypically and ultrastructurally (3, 14, 18). Hatoum et al. reported cervical lymphadenopathy in 80% of patients at the time of diagnosis. In the present case, involvement of the cervical lymph nodes was apparent at the time of diagnosis of the tumor (8, 19).

According to above discussion, a definitive diagnosis of salivary SmCC is not possible with only histopathological findings. Therefore, for confirming the histopathological diagnosis of neuroendocrine SmCC, IHC staining must be performed. Medical history, clinical examination, and image-based studies should also be considered to rule out metastatic SmCC (2).

In the current case, the most important differential diagnosis was metastatic carcinoma, but because of the lack of history of any other primary tumors, this probability was not confirmed. In order to exclude pulmonary SmCC, a complete chest examination with a CT scan was performed. Involvement of the lung was not apparent in the radiographic images of the chest. Negative immunohistochemical staining with S-100, LCA, CD99, and desmin helped to distinguish the present salivary SmCC from malignant melanoma, lymphoma, Ewing's sarcoma, and rhambdomyosarcoma, respectively.

Different studies have reported that SmCC of the salivary glands has a better outcome in comparison with pulmonary SmCC (1-3). However, local recurrence and distant metastases have been reported in more than 50% of patient after diagnosis (2, 9). In Jorcano et al.'s study, tumors with a diameter of larger than 3 cm were shown to have a poorer prognosis than smaller tumors. Therefore, larger sized tumors could be an indicator of poor prognosis. Additionally, they reported that tumors expressing more than four different neuroendocrine markers in comparison with those that expressed only two or three neuroendocrine markers were indicative of a better prognosis (9).

Due to the rarity of these tumors and the scant data about them, there is still controversy about the treatment regimen (3, 8). The current treatment of choice for SmCC is wide local excision of the tumor and ipsilateral cervical lymphadenectomy. In addition, adjuvant chemotherapy and radiotherapy may be warranted (3, 7). Chemotherapy is the chief choice treatment for patients with recurrence or metastasis, and in cases of advanced aggressive tumors (3).

Jorcano et al. demonstrated that the local recurrence rate in cases that have only been treated by surgery was 75%, whereas this rate is reduced to 20% in patients with a combination of surgery and radiotherapy. Furthermore, the survival rate of those that have been treated by surgery alone was lower than of those that used combined treatment (9). Therefore, combined treatment is recommended.

3.1. Conclusion

In conclusion, one relatively unknown case of small cell carcinoma in the oral cavity was introduced. The presentation of these cases can be helpful for the histopathological differential diagnosis of similar tumors.

References

1. van der Heijden HF, Heijdra YF. Extrapulmonary small cell carcinoma. *South Med J.* 2005;**98**(3):345–9. doi: 10.1097/01.SMJ.0000145724.40477.50. [PubMed: 15813162].
2. 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):1275–8. doi: 10.3892/ol.2014.2258. [PubMed: 25120705].
3. Lu CHCW, Chen C, Lin JT, Chan CH, Lee KD. Extrapulmonary small cell carcinoma. *Intern Med Taiwan J.* 2009;**20**:294–300.
4. Cimino-Mathews A, Lin BM, Chang SS, Boahene KD, Bishop JA. Small cell carcinoma ex-pleomorphic adenoma of the parotid gland. *Head Neck Pathol.* 2012;**6**(4):502–6. doi: 10.1007/s12105-012-0376-1. [PubMed: 22736150].
5. 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;**7**(3):295–303. doi: 10.1007/s12105-013-0431-6. [PubMed: 23456649].
6. Reis-Filho JS, Carrilho C, Valenti C, Leitao D, Ribeiro CA, Ribeiro SG, et al. Is TTF1 a good immunohistochemical marker to distinguish primary from metastatic lung adenocarcinomas? *Pathol Res Pract.* 2000;**196**(12):835–40. doi: 10.1016/S0344-0338(00)80084-9. [PubMed: 11156325].
7. Gnepp DR, Wick MR. Small cell carcinoma of the major salivary glands. An immunohistochemical study. *Cancer.* 1990;**66**(1):185–92. [PubMed: 1693875].
8. Singla A, Singla A, Gallagher R. A rare case and literature review of primary neuroendocrine carcinoma of the tonguedagger. *J Surg Case Rep.* 2014;**2014**(8) doi: 10.1093/jscr/rju084. [PubMed: 25148834].
9. Jorcano S, Casado A, Berenguer J, Arenas M, Rovirosa A, Colomo L. Primary neuroendocrine small cell undifferentiated carcinoma of the parotid gland. *Clin Transl Oncol.* 2008;**10**(5):303–6. doi: 10.1007/s12094-008-0203-z.
10. Olofsson J, Van Nostrand AW. Anaplastic small cell carcinoma of larynx. Case report. *Ann Otol Rhinol Laryngol.* 1972;**81**(2):284–7. [PubMed: 5027598].

11. Mills SE. Neuroectodermal neoplasms of the head and neck with emphasis on neuroendocrine carcinomas. *Mod Pathol.* 2002;**15**(3):264–78. doi: 10.1038/modpathol.3880522. [PubMed: 11904342].
12. Bahrami A, Truong LD, Ro JY. Undifferentiated tumor: true identity by immunohistochemistry. *Arch Pathol Lab Med.* 2008;**132**(3):326–48. doi: 10.1043/1543-2165(2008)132[326:UTTIBI]2.0.CO;2. [PubMed: 18318577].
13. Baca JM, Chiara JA, Strenge KS, Keylock JB, Jones CL, Harsha WJ. Small-cell carcinoma of the parotid gland. *J Clin Oncol.* 2011;**29**(2):34–6. doi: 10.1200/JCO.2010.29.1435. [PubMed: 20956630].
14. Huntrakoon M. Neuroendocrine carcinoma of the parotid gland: a report of two cases with ultrastructural and immunohistochemical studies. *Hum Pathol.* 1987;**18**(12):1212–7. [PubMed: 3679198].
15. Eversole LR, Knapp DR. Small cell carcinoma In: Surgical Pathology of the Salivary Gland, Eversole GM. Philadelphia: Saunders; 1991. pp. 432–8.
16. Kalhor N, Zander DS, Liu J. TTF-1 and p63 for distinguishing pulmonary small-cell carcinoma from poorly differentiated squamous cell carcinoma in previously pap-stained cytologic material. *Mod Pathol.* 2006;**19**(8):1117–23. doi: 10.1038/modpathol.3800629. [PubMed: 16680154].
17. Rossi G, Cavazza A, Marchioni A, Migaldi M, Bavieri M, Facciolongo N, et al. Kit expression in small cell carcinomas of the lung: effects of chemotherapy. *Mod Pathol.* 2003;**16**(10):1041–7. doi: 10.1097/01.MP.0000089780.30006.DE. [PubMed: 14559988].
18. Devoe K, Weidner N. Immunohistochemistry of small round-cell tumors. *Semin Diagn Pathol.* 2000;**17**(3):216–24. [PubMed: 10968707].
19. Hatoum GF, Patton B, Takita C, Abdel-Wahab M, LaFave K, Weed D, et al. Small cell carcinoma of the head and neck: the university of Miami experience. *Int J Radiat Oncol Biol Phys.* 2009;**74**(2):477–81. doi: 10.1016/j.ijrobp.2008.08.014. [PubMed: 19004574].