Head and Neck Pathol (2009) 3:163–168
DOI 10.1007/s12105-009-0114-5

CASE REPORT

Acinic Cell Carcinoma with Extensive Neuroendocrine Differentiation: A Diagnostic Challenge

Somak Roy · Kajal Kiran Dhingra · Parul Gupta · Nita Khurana · Bulbul Gupta · Ravi Meher

Received: 30 January 2009 / Accepted: 11 March 2009 / Published online: 26 March 2009

Abstract Primary salivary gland carcinoma with neuroendocrine differentiation is of rare occurrence, especially so in the parotid gland. Amongst the various reported primary tumors with neuroendocrine differentiation, acinic cell carcinoma (ACC) one such tumor. A 48 year old lady presented with a gradually increasing right infra-auricular swelling for a period of 1 year which enlarged suddenly in a short period. Contrast Enhanced Computed Tomography (CECT) suggested diagnosis of Pleomorphic Adenoma. Fine Needle Aspiration Cytology (FANC) yielded a cystic fluid suggesting a possibility of Warthin's tumor or Oncocytic lesion. Intraoperative findings were suggestive of a Warthin's tumor. Initial histopathological examination of the tumor was suggestive of neuroendocrine carcinoma. However, extensive sectioning revealed peripheral islands of ACC. Immunoexpression of S-100, Neuron specific Enolase (NSE), Chromogranin A and Synaptophysin confirmed the diagnosis. The possibility of neuroendocrine differentiation in a primary salivary gland tumor should be kept in mind whenever a salivary gland tumor shows only neuroendocrine histology.

S. Roy · K. K. Dhingra · P. Gupta · N. Khurana
Department of Pathology, Maulana Azad Medical College, New Delhi, India

B. Gupta · R. Meher
Department of Otorhinolaryngology, Lok Nayak Hospital, New Delhi, India

S. Roy (✉)
B-105, Kesar Garden Apartments, Sector-48, Noida, UP PIN-201303, India
e-mail: roys911@gmail.com

Keywords Neuroendocrine · Acinic cell · Warthin's · Chromogranin · Carcinoma · Parotid

Introduction

Primary salivary gland carcinomas with neuroendocrine differentiation are rare accounting for 3.5% of all malignant tumors and less than 1% of all carcinomas of parotid gland [1]. Nicod reported the first case of carcinoid tumor of the parotid gland in a 51 year old lady [2]. Following this there have been occasional reports of round cell tumors of the parotid gland and minor salivary glands with very few reports of primary neuroendocrine tumor [1–4]. Amongst the various primary tumors showing neuroendocrine differentiation, ACC has been documented in very few studies [5–7].

Case Report

A 48 year old lady presented to the Ear Nose and Throat outpatient department with a small, painless, right sided infra-auricular swelling for 1 year which had suddenly increased in size in the past 1 month (Fig. 1). She denied any loss of weight or similar swelling elsewhere in the body. Local examination revealed a round, well defined, firm, non-pulsatile swelling fixed to the underlying structures measuring 3 × 3 cms located in tail of parotid. The overlying skin was normal and free from the swelling. There were no palpable cervical, or supraclavicular lymph nodes.

Contrast enhanced CT (CECT) scan revealed a well defined, homogenously enhancing soft tissue mass, measuring 3.5 × 3 × 2.5 cms, in the superficial lobe of the

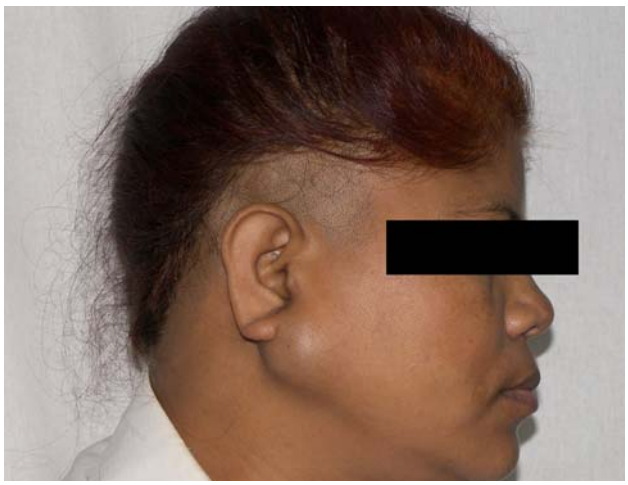

Fig. 1 Right infra-auricular, painless swelling 4.5 × 3.5 cms

right parotid gland causing medial displacement of the retromandibular vein. A small focus of calcification was also visualized. The deep lobe of the right parotid, left parotid gland and bilateral carotid sheath structure did not reveal any abnormality (Fig. 2). No significant neck adenopathy was observed. A diagnosis of pleomorphic adenoma was suggested based on CECT findings.

On follow-up visit the swelling increased in size with prominent cystic change. FNAC suggested it to be an Oncocytic tumor or a Warthin's tumor.

Patient was taken up for right superficial parotidectomy by modified Blair's incision. During surgery a cystic swelling was found to be involving the superficial lobe of

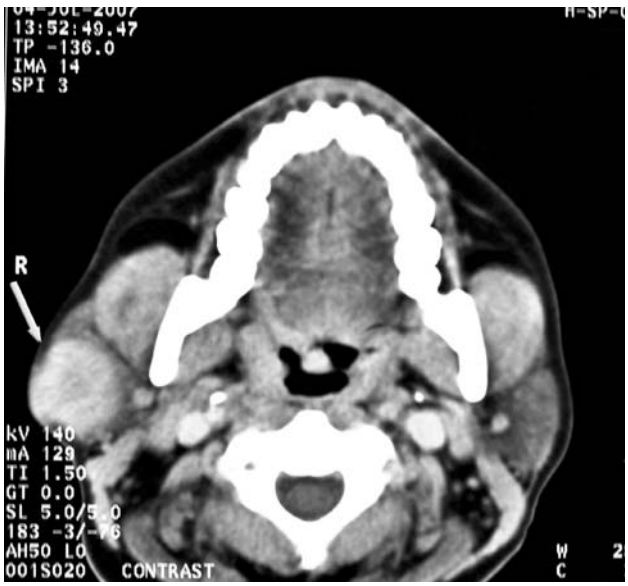

Fig. 2 CECT scan showing a well defined, homogenously enhancing soft tissue mass, measuring 3.5 × 3 × 2.5 cms, in the superficial lobe of the right parotid gland with displacement of the retromandibular vein

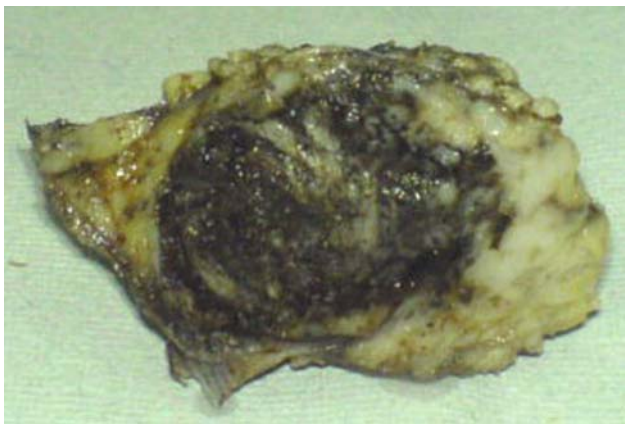

Fig. 3 Cut section showing a well defined nodule (3.3 × 2.9 × 2.2 cms), which is grey white to dark in color with areas of congestion and surrounding thin rim of normal salivary gland

parotid which was excised with a margin of normal surrounding glandular tissue. The underlying facial nerve was normal. The post operative period was uneventful.

On gross examination, the specimen measured 3.8 × 3.2 × 2.5 cms in size with focal areas of congestion. On cut section a well defined nodule was identified measuring 3.3 × 2.9 × 2.2 cms, which was grey white with focal areas of hemorrhage (Fig. 3). Also seen was a small, already opened up, part of a cystic structure measuring 1 × 1 × 0.7 cms filled with multiple, small, friable, whitish material. All resection margins were grossly free of tumor.

Microscopically, a highly cellular tumor was seen, comprised of small and large cells arranged in prominent organoid pattern, nests, trabeculae and sheets. The nests of cells were separated by thin to thick, hyalinised fibrous septae (Fig. 4). The individual cell had a centrally placed,

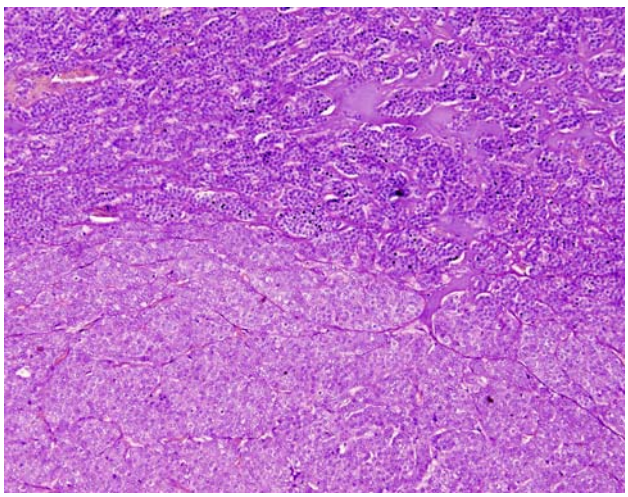

Fig. 4 Tumor cells arranged in organoid and nesting pattern, separated by thin and think hyalanised fibrous septae. Both small and large cell neuroendocrine pattern can be identified. (H&E, 100×)

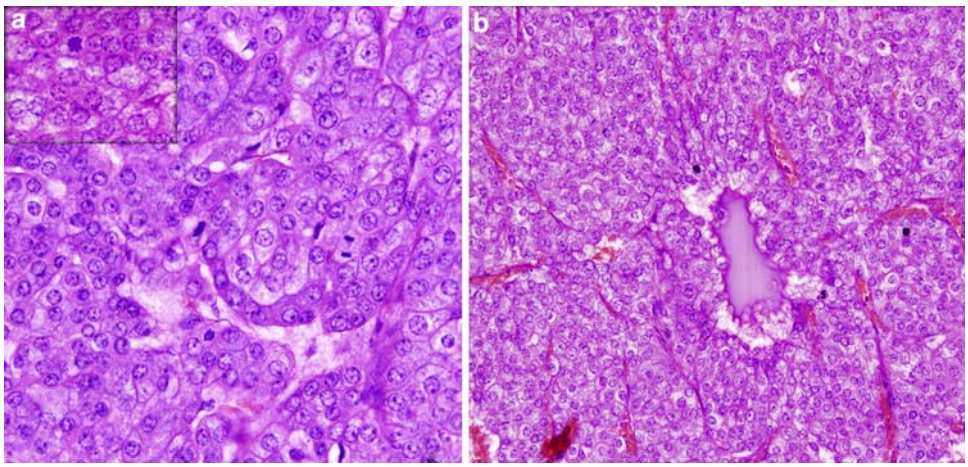

Fig. 5 **a** Tumor cells show large round, uniform nuclei with stippled nuclear chromatin. Moderate amount of finely granular and eosinophilic cytoplasm can be seen with well defined cytoplasmic membranes. Mitotic figures both typical and atypical can be seen (H&E, 600×). Inset—Showing atypical mitosis (H&E, 600×). **b** Small microcystic areas seen amidst tumor cells filled with pale eosinophilic material (H&E, 250×)

round nucleus with coarsely stippled nuclear chromatin. Occasional nuclei showed single, central to eccentrically placed nucleolus. The cells displayed moderate to abundant amount of deeply eosinophilic and finely granular cytoplasm with well defined cytoplasmic borders. Both typical and atypical mitoses were seen throughout the tumor (Fig. 5a, inset). Few areas showed presence of microcystic spaces filled with pale, eosinophilic secretions lined by the tumor cells (Fig. 5b). Prominent thin walled, elongated blood vessels were also seen along with multiple foci of hemorrhage. Both the small and large cell neuroendocrine pattern was seen in the same tumor (Fig. 4). Further sections from the mass revealed variable sized clusters of cells arranged in sheets, with centrally placed nucleus and abundant cytoplasm studded with numerous fine, basophilic granules suggestive of ACC (Fig. 6), which was confirmed by PAS stain with and without diastase pretreatment. However, it was seen focally at the periphery of the tumor mass. The two different tumor areas were not distinctly separate from each other. The tumor cells strongly expressed S-100, NSE, Chromogranin A, and Synaptophysin (Fig. 7a–d) and were negative for epithelial membrane antigen and cytokeratin. The acinic cell tumor component showed focal positivity for cytokeratin. Based on the histomorphological and immunohistochemical features a diagnosis of ACC with extensive neuroendocrine differentiation was made. The tumor was seen to focally involve the deep resection plane and one of the lateral margins of resection.

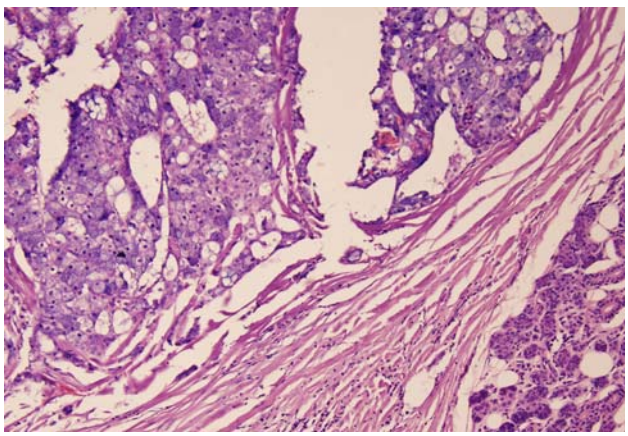

Fig. 6 Tumor at the periphery shows cells in clusters and sheets with centrally placed small nuclei and abundant cytoplasm studded with fine basophilic granules suggestive of acinic cell carcinoma (H&E, 250×)

Patient was followed up subsequently after 3 months with no clinical evidence of recurrence of the tumor and a good healing of the surgical wound. Since the deep plane and lateral resected plane were microscopically involved, the patient was referred to the Department of Radiotherapy for further evaluation and management of possible residual tumor. On further follow-up after 6 months from the initiation of radiotherapy, there was no clinical evidence of recurrence of the tumor.

Discussion

Primary carcinoma of salivary gland with neuroendocrine differentiation is rare accounting for only 1% of all parotid gland tumors [1]. Neuroendocrine tumors of the parotid gland that have been reported previously were most commonly metastatic or seen in association with co-existing carcinoid tumor elsewhere [1–4]. The various primary salivary gland carcinomas that have been reported to show positivity for neuroendocrine markers include a large majority of small cell carcinoma, occasional cases of adenocarcinoma, Warthin's tumor, adenoid cystic carcinoma, and ACC [5–8].

ACCs occur usually in the 3rd and 4th decade with a mean age of 44 years and shows predilection to occur in females [9, 10]. Our patient was a 48 year old lady. Most commonly the parotid gland is affected (84%) [9] as was in our case, however it is also known to occur in

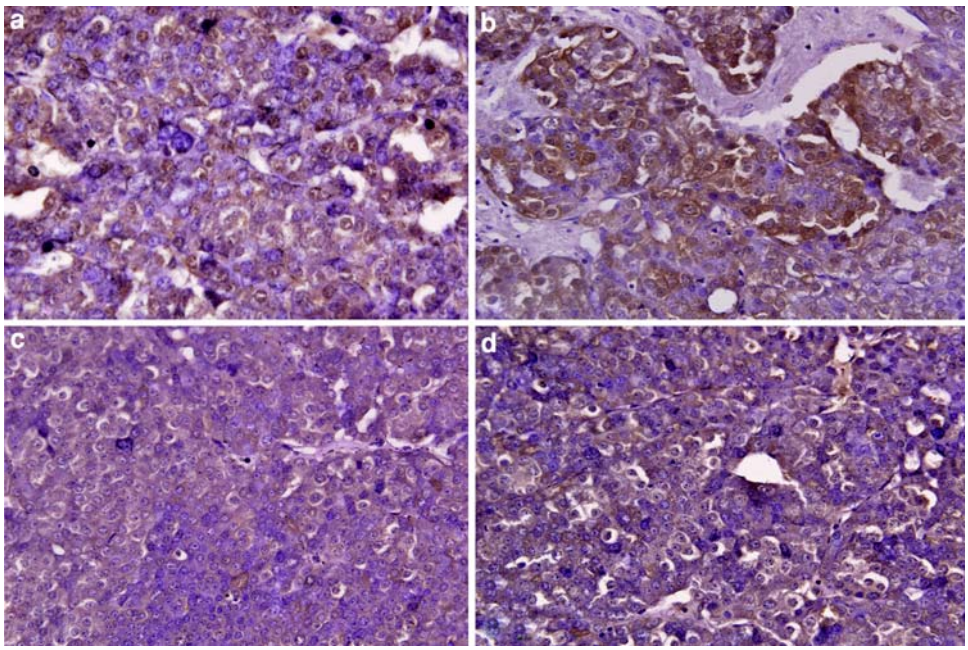

Fig. 7 **a** Strong cytoplasmic positivity for S-100 (DAB chromogen, 400×). **b** Strong cytoplasmic positivity for Neuron Specific Enolase (DAB chromogen, 400×). **c** Strong granular cytoplasmic positivity for Chromogranin A (DAB chromogen, 400×). **d** Strong cytoplasmic positivity for Synaptophysin (DAB chromogen, 400×)

submandibular and minor salivary glands [9]. Clinically, it presents as a slowly growing painless or painful mass with infrequent facial nerve involvement (5–10%) and pursues a protracted clinical course [9]. Our patient had a gradually increasing painless swelling with rapid increase in size of recent onset without clinical and intraoperative evidence of facial nerve involvement.

ACCs are usually rounded and partially or completely encapsulated with predominant solid, brown cut surface with or without cystic areas [9, 10]. In our case the tumor was predominantly solid with a small superficial cyst filled with clear fluid. ACCs have been reported to mimic pleomorphic adenoma grossly especially if it is recurrent [10].

Microscopically, the tumor is comprised of variably sized lobules of neoplastic cells with broad fronts of invasion [9]. The cells have a small central to eccentrically placed nuclei with a finely granular to clear cytoplasm—features suggestive of differentiation towards the ductal and acinar cells of normal salivary gland. The granules are fine, numerous, basophilic, and PAS positive [9, 10]. The granularity of the cells is markedly variable in the same tumor field [9]. Similar features were seen in the ACC component of the tumor in our case. Immunohistochemically, the tumor cells express Cytokeratin (especially low molecular weight), Carcinoembryonic antigen and amylase [9]. In our case the cells of ACC component showed focal positivity for Cytokeratin.

ACCs expressing neuroendocrine markers have been reported. Although not yet accepted as a distinct clinicopathological entity, some studies have reported neuroendocrine differentiation in ACC based on immunohistochemistry and ultra structural studies [5, 7].

Hayashi et al. [5] in 1987 performed a study of expression of neuropeptides in various parotid gland tumors which included 11 cases of ACCs along with other benign and malignant tumors. They reported the expression of Vasoactive Intestinal Polypeptide (VIP) in all the 11 cases of ACCs however was not seen in any other parotid gland tumor. The cells of the ACCs stained with Grimelius impregnation and six of these cases on ultra structural study demonstrated presence of large dense core granules along with smaller numerous secretory granules and well developed golgi apparatus and rough endoplasmic reticulum.

In another study by Hayashi et al. [6] in 1990, they studied the expression of neuroendocrine markers—NSE and Leu-7 in various parotid gland tumors. Included in this study were 12 cases of ACC of which seven expressed only Leu-7 only. Other tumors of the salivary gland expressed either or both NSE and Leu-7.

Ito et al. [7] in 1990 reported a case of ACC with neuroendocrine differentiation in the parotid gland. Light microscopy showed a classical clear cell ACC. Staining for Grimelius impregnation and ultra structural evidence of dense core granules were suggestive of neuroendocrine features in the cells of the tumor.

In all the above studies, the evidence of neuroendocrine differentiation was evident only on special staining, immunoexpression of neuropeptides and ultra structural morphology. However, none of the cases showed any histomorphological evidence of neuroendocrine differentiation. The studies conducted by Hayashi et al. [5, 6], screened for neuropeptide expression in various tumors of the parotid gland. None of the cases of ACC in their

studies showed histomorphological features of neuroendocrine tumor. Similarly the reported case by Ito et al. [7] had a histomorphology, compatible with classical clear cell ACC without any histological feature suggestive of neuroendocrine differentiation.

However, in our case the diagnosis of this tumor was very intriguing. Preoperatively there were varied diagnosis of pleomorphic adenoma radiologically and oncocytic tumor versus Warthin's tumor on cytopathology. Intraoperatively, the suspicion of Warthin's tumor was high. Even the initial histological sections were suggestive of a very rare diagnosis of primary neuroendocrine tumor. However, after further sectioning of the tumor mass in search of other commoner primary tumors, small areas of ACC was documented. Such extensive degree of neuroendocrine differentiation in an ACC, morphologically and immunohistochemically, to the extent as to mimic a primary neuroendocrine tumor of the parotid gland, has not been reported previously to the best of our knowledge.

A possibility of peripheral entrapped acinic cell with primary neuroendocrine tumor was also ruled out; since both the morphological areas of the tumor were in gradual continuity with each other and neither did the acinic cells appear to be compressed at the periphery.

Hayashi et al. used Leu-7, NSE, and VIP to demonstrate the neuroendocrine differentiation [5, 6]. In our case confirmation of neuroendocrine differentiation was done using Synaptophysin, NSE, Chromogranin A, and S-100.

A possibility of divergent differentiation or de-differentiation has been discussed previously. De-differentiated ACC is an aggressive form of the tumor requiring adjuvant treatment, carrying a poor prognosis. It is histologically characterized as a composite tumor with ACC along with a poorly or undifferentiated carcinoma [11]. Ito et al. [7] suggested that a tumor arising from a common stem cell can lead to divergent differentiation into both ACC and neuroendocrine tumor in the same mass. However, in our case, there were no areas showing poor differentiation or markedly anaplastic morphology. Also after 6 months of follow-up the patient had no evidence of tumor recurrence. The concept of divergent differentiation could be a possible explanation for the phenomenon, however requiring further studies on these tumors.

Grading of ACC has been attempted based on histomorphological features, segregating them into well, moderately and poorly differentiated tumor [11, 12], showing good prognostic correlation. However, it does not account into presence of neuroendocrine features as affecting the grading of the tumor. Also the presented tumor is very rare, making it difficult to assess the impact on grading and prognosis.

Tumors with similar morphology have been reported in the pancreas also. The reported tumors demonstrated acinar cell tumors with variable component of neuroendocrine differentiation. The neuroendocrine nature of the cells was proven predominantly on the basis of immunohistochemistry and electron microscopy [13–15]. Some authors have reported that the presence of neuroendocrine differentiation in pancreatic acinar cell carcinoma carries a better prognosis that the tumor without it [15].

Conclusion

Primary neuroendocrine tumors of the parotid gland are of rare occurrence. Hence when a salivary gland tumor shows only neuroendocrine histology, the possibility of primary salivary gland tumor with neuroendocrine differentiation should be kept in mind and tumor extensively sampled to hunt for such a tumor. One should also be aware of the fact that ACCs can show extensive neuroendocrine differentiation so much so as to mimic a primary neuroendocrine tumor of the parotid gland. Since there are very few cases of neuroendocrine differentiation reported in acinic cell tumor, a definite comment on prognostic outcome is not possible. Further studies with long follow-up of these patients need to be done to understand the biological behavior of this special variant of ACC.

References

1. Pontius AT, Ducic Y. Metastatic neuroendocrine tumors of the parotid gland. Am J Otolaryngol. 2004;25:129–33.
2. Eusebi V, Pileri S, Usellini L, et al. Primary endocrine carcinoma of the parotid salivary gland associated with a lung carcinoid: a possible new association. J Clin Pathol. 1982;35:611–6.
3. Nagao T, Sugano I, Ishida Y, et al. Primary large-cell neuroendocrine carcinoma of the parotid gland: immunohistochemical and molecular analysis of two cases. Mod Pathol. 2000;13(5):554–61.
4. Modlin IM, Shapiro MD, Kidd M. Primary carcinoid tumor of the parotid gland: a case report and review of literature.
5. Hayashi Y, Nishida T, Yoshida H, et al. Immunoreactive vasoactive intestinal polypeptide in acinic cell carcinoma of the parotid gland. Cancer. 1987;60:962–8.
6. Hayashi Y, Deguchi H, Nakahata A, et al. Immunopathological study of neuropeptide expression in human salivary gland neoplasms. Pathobiology. 1990;58:212–20.
7. Ito K, Kakudo K, Mori I, et al. Neuroendocrine differentiation in a case of acinic cell carcinoma of the parotid gland. Acta Pathol Jpn. 1990;40:279–87.
8. Hayashi Y, Nagamine S, Yanagawa T, et al. Small cell undifferentiated carcinoma of the minor salivary gland containing exocrine, neuroendocrine, and squamous cells. Cancer. 1987;60:1583–8.
9. Cheuk W, Chan JKC. Salivary gland tumors. In: Fletcher CDM, editor. Diagnostic histopathology of tumors. 2nd ed. London: Churchill Livingstone; 2000. p. 231–305.
10. Sternberg SS, editor. Histology for pathologists. 2nd ed. Philadelphia (PA): Lippincott-Raven; 1997.
11. Huvos AG, Paulino AFG. Salivary gland. In: Mills SE, Carter D, Reuter VE, et al., editors. Sternberg's diagnostic surgical

pathology, vol. 2. 4th ed. India: Lippincott Williams & Wilkins; 2004. p. 933–60.
12. Batsakis JG, Chinn EK, Weimert TA, et al. Acinic cell carcinoma: a clinicopathologic study of thirty-five cases. J Laryngol Otol. 1979;93:325–40.
13. Minakawa K, Oka K, Nihei T, et al. Pancreatic endocrine tumor with partial acinar cell differentiation. APMIS. 2006;114:720–5.
14. Tobita K, Kijima H, Chino O, et al. Pancreatic acinar cell carcinoma with endocrine differentiation: immunohistochemical and ultrastructural analyses. Anticancer Res. 2001;21:2131–4.
15. Martin SK, Agarwal G, Lynch GR. Subcutaneous fat necrosis as the presenting feature of a pancreatic carcinoma: the challenge of differentiating endocrine and acinar pancreatic neoplasms. Pancreas. 2009;38:219–22.