

Large Cell Neuroendocrine Carcinoma of Parotid Gland: A Diagnostic Dilemma among High Grade Carcinomas of Parotid Gland - Case Report

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Abstract

Introduction: Large cell neuroendocrine carcinoma is a distinct clinicopathological entity which is extremely rare among salivary glands. Fine needle aspiration cytology is a valuable tool in the diagnosis of salivary gland tumors but due to extreme rarity of large cell neuroendocrine carcinoma and high grade cytological features this tumor is usually not in the list of high grade carcinomas differentials. We have documented a case of large cell neuroendocrine carcinoma that was misdiagnosed initially as tuberculous parotitis and later on as large cell high grade carcinoma on fine needle aspiration cytology.

Case report: A 45 year old male with a painful lump at right parotid and facial nerve weakness was initially misdiagnosed as tuberculous parotitis and treated with anti-tuberculous therapy. Based on fine needle aspiration cytology, he has been treated as high grade carcinoma of parotid. Radical parotidectomy and neck dissection from level 1-5 was performed to be followed by post-operative radiotherapy. Currently patient is alive without disease and on regular follow up.

Conclusion: Due to varied morphological and biological behavior of large cell neuroendocrine carcinoma, early diagnosis seems to be an important prognostic factor. Surgery should be considered as the mainstay of treatment supplemented by postoperative radiotherapy and chemo radiotherapy.

Keywords: Large cell neuroendocrine carcinoma; Salivary glands; Fine needle aspiration cytology

Abbreviations: LCNEC: Large Cell Neuroendocrine Carcinoma; FNAC: Fine Needle Aspiration Cytology; PORT: Post-Operative Radiotherapy; CRT: Chemo-Radiotherapy; IJV: Internal Jugular Vein; ICA: Internal Carotid Artery;

ECA: External Carotid Artery; DSS: Disease Specific Survival

Introduction

Large cell neuroendocrine carcinoma (LCNEC) is a newly proposed clinicopathological entity first described in the lung but also reported in extra pulmonary sites such as cervix, thymus and colon. Among salivary glands they are extremely rare. Kawartani et al. [1] reported only 8 cases in the PubMed search in last 40 years. It is very important to distinguish large cell neuroendocrine carcinoma from other carcinomas of the parotid gland such as High grade mucoepidermoid carcinoma, salivary duct carcinoma, carcinoma ex pleomorphic adenoma and squamous cell carcinoma because of aggressive behavior, high propensity for local recurrence, cervical node and distant metastases.

Fine needle aspiration cytology (FNAC) is still a valuable tool in the diagnosis of salivary gland tumors having significant sensitivity and specificity. Because of the extreme rarity of large cell carcinoma and high grade cytological features this tumor is usually not in the list of high grade carcinomas differentials [2].

Recently we have encountered a case of LCNEC that was misdiagnosed initially as Tuberculous Parotitis and later on as High grade carcinoma on FNAC followed by Parotidectomy and proven out to be primary Large cell NEC of parotid.

Case Report

A 45 year known hypertensive old male was referred to the Head and Neck Oncology Department, Shaukat Khanum Memorial Cancer Hospital with a fixed painful lump at right parotid region that has shown sudden growth over 2 weeks. He had a past history of right pre auricular swelling that was started 5 months back which gradually increased in size,

became painful 4 months back and using analgesics did not provide any benefit. He noticed facial weakness 3 months back and was treated for Bell's palsy by some outside physician. FNAC outside showed caseating granulomas suggesting it to be tuberculous parotitis for which anti-tuberculous therapy was started before he reported to our walk in clinic. FNAC at our hospital shows high grade parotid carcinoma.

Magnetic resonance imaging (MRI) scan (**Figure 1**) showed an infiltrative right parotid mass involving both superficial and deep lobes with extra capsular extension. The scan also showed involvement of right masseter and medial pterygoid muscle. Enhancing tumor was also abutting right carotid sheath/right cervical internal carotid artery (ICA) without radiological criteria for encasement. The internal jugular vein (IJV) was occluded below the level of the mass possibly due to a large necrotic lymph node. Cervical lymphadenopathy was obvious with the largest right level II node measuring 2.7 cm in long axis and another node overlying the parotid gland extending into the dermis and subcutaneous tissue measuring 1.5 cm. Chest x-ray findings were unremarkable.



Figure 1 STIR sequence showing infiltrative right parotid mass involving both superficial and deep lobes with extra capsular extension.

Right total parotidectomy with overlying skin was done en bloc with neck dissection (level I-V) using modified Blair incision and cervico-fascial advancement to cover the defect. Intraoperative findings were a locally advanced tumor approaching ICA in pre-styloid space infiltrating overlying skin with multiple enlarged nodes at right level II. Tumor was removed intact without spillage but right external carotid artery (ECA), facial and spinal accessory nerve could not be preserved due to involvement by the disease. Post-operatively shoulder and lip physiotherapy and eye-care were taken care of.

The final pathology report was large cell neuroendocrine carcinoma 9.5 cm with all margins free of tumor. Regional metastasis along with Perineural invasion (PNI) was present with 9 out of 49 lymph nodes harboring metastasis without extra nodal extension. Microscopically, sections revealed

tumor forming nests and sheets composed of large cells with round to ovoid nuclei (**Figure 2**), prominent nucleoli and moderate amount of clear to eosinophilic cytoplasm (**Figure 3**). The tumor also showed areas of necrosis and increased mitotic activity. Immunohistochemical stains were performed and only CD56 was positive while it was negative for LCA, Cytokeratin, p63, CD30, HMB45, CK7, GCDFP15, CD138, S100 and synaptophysin. Positron emission tomography-computed tomography (PET-CT) scan was performed to rule out primary where liver shows homogenous uptake with reference standardized uptake values (SUV) of 2.5. Spleen, pancreas, bilateral adrenals and kidneys were unremarkable. No suspicious pulmonary nodularity was seen. Patient was offered post-operative radiotherapy (PORT) with 60 Grey/30 fractions of 2 Grey/fraction in 6 weeks and currently on 3 monthly follow up during the first year.

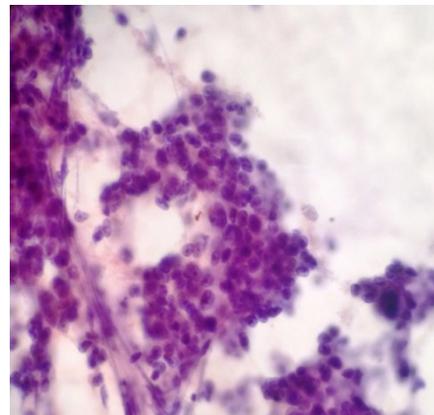


Figure 2 (PAP stain 400X) Cells displaying variation in size and shape with nuclear hyperchromasia and prominent nucleoli.

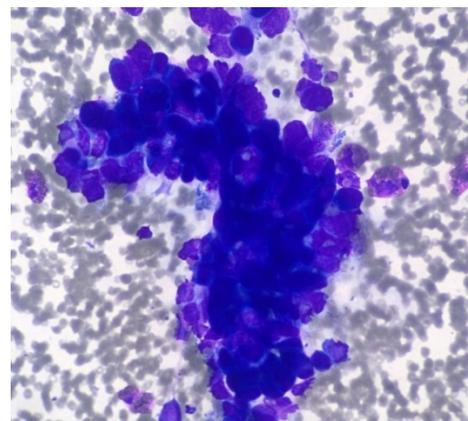


Figure 3 (Giemsa Stain) Clusters of cohesive nests of large round to oval cells with high nucleus to cytoplasmic ratio and moderate amount of cytoplasm.

Discussion

Tumors with neuroendocrine morphology are a distinct subset of neoplasms that share specific morphologic, histochemical, Immunohistochemical, ultrastructural, and molecular characteristics. These tumors include paraganglioma, well-differentiated neuroendocrine carcinoma (or typical carcinoid), moderately differentiated neuroendocrine carcinoma (or atypical carcinoid), small cell neuroendocrine carcinoma, and large cell neuroendocrine carcinoma (LCNEC) [3]. The first report of LCNEC in the head and neck was published by Hui et al. [4] in 1990 and at that time the authors used the term undifferentiated carcinoma. As a highly aggressive malignancy, this tumor attracts a significant attention and is in focus of considerable discussion recently also in head and neck area [5-10]. Larynx is the most common head and neck subsite involved by these tumors followed by parotid gland [9, 10]. In 2010, the World Health Organization (WHO) updated its classification of NET based on tumor site of origin, clinical syndrome, and differentiation. Histopathological features of NEC are organoid nesting, palisading, rosette trabeculae, large cell with a polygonal shape, relatively low nuclear to cytoplasmic ratio, frequent necrosis mimicking non SCC and positive neuroendocrine Immunohistochemical markers [11]. CD 56, synaptophysin and Chromogranin are the most specific immunomarkers of all. Immunohistochemical staining showed positivity for CD 56 in our case as it has 54% reported immune reactivity and demonstrates poor differentiation of the tumor as well (**Figure 4**) [12].

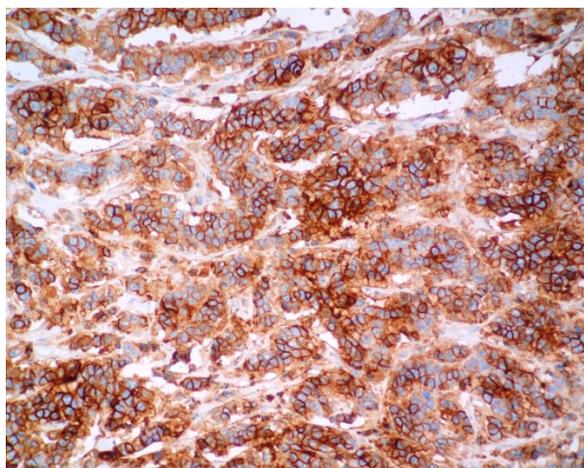


Figure 4 CD 56 stain show diffuse strong cytoplasmic staining.

Management guidelines still need more clinical trials to develop a consensus as LCNEC is a rarity and has varied morphological and biological behavior between small cell carcinoma and atypical carcinoid. Early diagnosis seems to be an important prognostic factor. Kawartani et al. [1] have found 7 reported cases of Salivary gland neuroendocrine carcinoma in their PubMed search between 1975 and 2011. FNAC findings were mostly undifferentiated and poorly differentiated carcinoma. Van Der Laan et al. [10] in his meta-analysis of 436

cases of neuroendocrine carcinoma of larynx has documented 5 year Disease specific survival (DSS) to be 15% for large cell neuroendocrine carcinomas.

For Large cell neuroendocrine carcinoma of Head and Neck due to their aggressive behavior and poor outcome, trimodality therapy seems to be the suitable action. For a localized disease, Surgery may be the mainstay of treatment supplemented by postoperative radiotherapy (PORT) and chemo-radiotherapy (CRT) but a larger scale study with a good sample size is advised to establish guidelines.

Conflict of Interest

The authors declare that they have no competing interests.

Author's Contribution

All authors read and approved the final manuscript. AJ and SRH has supervised the study. MF and IH have done the literature review and written the manuscript. OW have done the histopathological and immunoassay stuff. MT has contributed in references.

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