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NEUROENDOCRINE TUMORS PRESENTING AS CERVICAL LYMPHNODE METASTASIS OF UNKNOWN ORIGIN: A CASE SERIES

Oncology

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ABSTRACT

Neuroendocrine tumors constitute a group of tumors that originate from neuroendocrine cells throughout the body and constitute 2% of all malignancies. This study outlines 3 cases presenting as cervical lymphnode metastasis without known primary tumor at our institute which turned out to be neuroendocrine carcinoma.

KEYWORDS

Neuroendocrine tumors (NET), metastasis of unknown origin (MUO), Neuroendocrine carcinoma (NEC), Fluorodeoxy glucose (FDG), Positron emission tomography (PET) combined CT (computed tomography)

1. INTRODUCTION

Metastasis of unknown origin is the presentation of metastatic neck lymphadenopathy without the development of an index primary tumour within a subsequent 5 year period. The incidence of MUO is about 5% in head and neck, NET with epithelial differentiation occurs commonly in larynx[1], NETs accounts for 3% of all carcinoma of unknown origin[2], but NET presenting as neck and mediastinal metastasis constitute about 8.7%[3,4]. According to WHO classification (2017), neuroendocrine tumors are broadly divided into three grades which includes well differentiated, moderately differentiated and poorly differentiated categories[5].

1. Well differentiated (tyoical carcinoid, grade 1)
2. Moderately differentiated (atypical carcinoid, grade 2)
3. Poorly differentiated (small cell and large cell neuroendocrine NEC, grade 3)

Both degree of differentiation and proliferation index are considered as prognostic factors in neuroendocrine tumors. We encountered three cases of neuroendocrine carcinomas presenting as cervical lymphnode metastasis without any identifiable primary in a period of one year.

2. CASE REPORTS

2.1 CASE 1

A 62 year old male presented with bilateral neck swelling of 2 months duraion. He had history of pain associated with it. There was no history dysphagia, change in voice and any other systemic symptoms. On examination multiple enlarged right level II to IV lymph nodes with reduced mobility and left level II 4x3cm lymph nodes were noted. Fine needle aspiration cytology of swelling was done which showed metastasic neuroendocrine tumor with grade 3 differentiation. Routine metastatic work up was done. Panendoscopic examination revealed no primary in upper aerodigestive tract. On PET CT scan FDG avide conglomerate lymph node mass was seen involving right level II to IV neck, indenting right common carotid artery and external carotid artery. Right internal jugular vein thrombosis was noted. A similar FDG avid left level II node was seen.

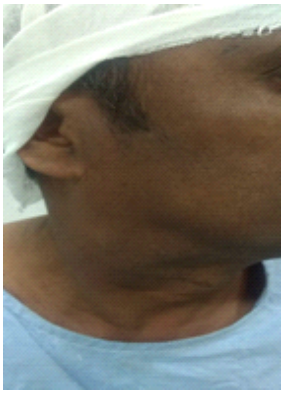

FIGURE 1: Preoperative image of right cervical mass

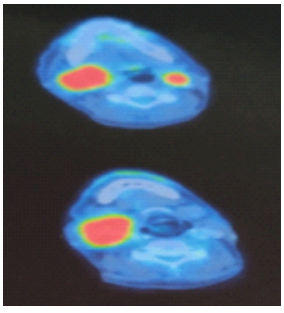

FIGURE 2: PET scan showing FDG avid cervical mass

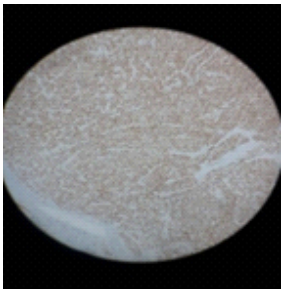

FIGURE 3: Immunohistochemistry showing positivity for ki67 labelling index

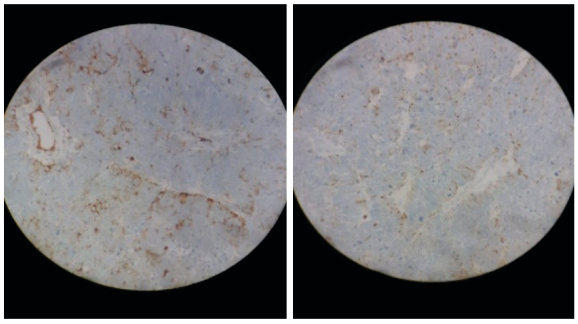

FIGURE 4: positive staining for chromogranin and cytokeratin

No other primary was detected. Right Radical neck dissection and left modified radical neck dissection was done. Histopathology report showed metastatic neuroendocrine carcinoma with squamous elements and with perinodal spread. Immunohistochemistry showed positivity for chromogranin and synaptophysin. Ki67 index was 57%. Postoperatively adjuvant chemo-radiotherapy was given.

2.2 CASE 2

A 51 year old male presented with left sided neck swelling of 3 months duration. On examination multiple level 2 to 3 N3b lymph nodes were noted. Panendoscopy report was negative for primary tumor. Routine

metastastic workup with PET scan showed multiple lymph nodes abutting the great vessels and extending to involve both lobes of parotid. Left extended radical neck dissection with conservative total parotidectomy was done. Pathology report showed metastatic poorly differentiated neuroendocrine carcinoma with extranodal extension. Detailed special stains showed positivity for chromogranin and synaptophysin with ki67 index of 67%. Post operative, patient underwent adjuvant concurrent chemoradiotherapy.

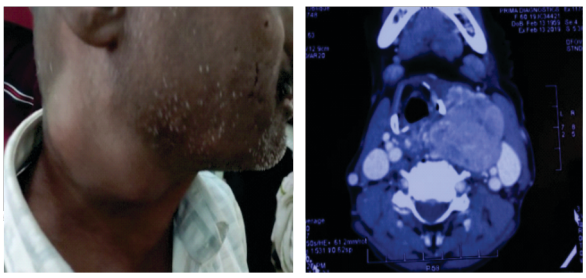

FIGURE 5 (a) and (b): showing preoperative clinical picture and imaging of left cervical metastasis

2.3 CASE 3

A 62 year old male presented with left sided neck swelling for 3 months with history of rapid increase in size of swelling and ulceration. On examination multiple matted right levels II to IV lymph nodes with restricted mobility and skin ulceration was noted. Routine metastatic work up didn't show up any primary.

Fine needle aspiration cytology of the nodes showed features of poorly differentiated neuroendocrine carcinoma. Contrast enchanced radioimaging of neck showed multiple congolomerate nodes compressing IJV and encasing the carotid vessels more than 270degree. As the mass was unresectable and encircling the major vessels, patient was sent for palliative chemotherapy. But due to advanced stage of the disease, patient expired within 6 months of starting treatment.

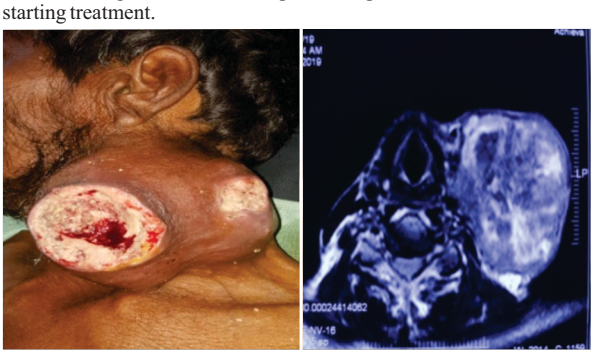

FIGURE 6 (a) & (b): Showing ulcerated matted left neck nodes which on imaging shows unresectable mass encircling major vessels

4. DISCUSSION

In our study, we have reported three cases of neuro-endocrine carcinomas presenting as metastatic cervical lymphadenopathy without any identifiable primary. Neuroendocrine carcinomas are neuroendocrine neoplasia of epithelial origin and derives from diffuse neuroendocrine system. It constitutes 1% of mucosa associated head and neck carcinomas[6]. The most common sites of NEC in head and neck region is larynx followed by salivary glands[7]. Meacham R et al study showed most common sites as salivary glands,paranasal sinuses and supraglottis[8].

Lymph node metastasis of NEC from unknown primary is a rare entity. Eusebi et al in 1997 published an article in which he reported eight cases of neuroendocrine tumors presenting as metastatic lymphadenopathy without any primary. Out of eight cases, five had inguinal, two had axillary and one had submandibular lymphadenopathy[9]. Lymph node metastasis is high in moderately differentiated grade laryngeal NEC while poorly differentiated lesions usually develops distant metastasis in more than 90% of cases[10]. Paranasal sinus sites has propensity for both regional and distant metastasis[11,12]. In a study by Batsakis JG et al the locoregional metastasis in well differentiated NEC was reported to be ranging from 30.7% to 33%[13,14]. Among the moderately differentiated group the values are 43% lymphatic metastasis and 44% distant metastasis[15]. The poorly differentiated grade rarely spreads to lymph nodes[10]. In our case series all the three cases had poorly differentiated grade NEC but was not showing any distant metastasis evidence on our routine work up. All the cases were having history of rapidly increasing mass showing the aggressive behavior of G3 variant and two cases that were operated showed extranodal extension on final pathology report.

Among the pathological prognostic factors, other than tumor grade, mitotic activity and ki67 labeling index were also considered as relevant. But currently, data available regarding ki67 index in head and neck is lacking to draw proper conclusions[16]. In a study by Kao et al 23 NEC cases of head and neck were classified based on 2010 WHO classification these values as:[17]

1. Typical carcinoid (well differentiated) : mitotic activity < 2/10 hpf and / ki 67 index </= 2%
2. Atypical carcinoid (moderately differentiated): mitotic activity 2 to 10/ 10 hpf and ki67 index 3 to 20%
3. Small cell and large cell NET. (Poorly differentiated): mitotic activity >10/10 hpf and ki67 index >20%.

All the three cases in our series had ki67 index more than 20% showing high proliferation index thus reflecting poor prognosis.

All our cases underwent PET CT scan or CECT scan to check for the extent of nodal involvement and in identifying any primary lesions. FDG PET scan has a specific role in imaging poorly differentiated NETs with more biologically aggressive behavior[11].

The treatment of poorly differentiated NEC historically consisted of radiation and or chemotherapy. In our case series two cases were surgically salvageable with proper plane of dissection. Hence they underwent neck dissection followed by postoperative adjuvant chemotherapy and radiotherapy which gave us best results in the setting of G3 grade tumors. As one case was surgically not salvageable due to encasing of the great vessels, palliative chemotherapy was advised and the patient survived only for 6 months.

5. CONCLUSION

Studies regarding NEC presenting as metastasis of unknown origin in neck is very rare to the best of our knowledge. In this study we could demonstrate the rare presentation of NEC as cervical metastasis. All the three cases had G3 differentiation with high proliferation index showing aggressive behavior and poor prognosis. As the size of our case series is small, limited conclusion could be drawn regarding this rare presentation. The treatment decisions for our patients were made on individual basis, based on resectability criteria. Hence further studies with larger case series are awaited for better understanding of this topic.

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