CASE REPORT

Cervical ganglioneuroma in collision with a metastatic undifferentiated carcinoma

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ABSTRACT

Cervical ganglioneuromas are extremely rare with approximately six case reports. The current report highlights a unique collision tumor between a cervical ganglioneuroma and a metastatic undifferentiated carcinoma arising from a primary gingival mass. A 53-year-old male presented with a 2 cm left gingival mass that was excised and treated with systemic chemotherapy. Consequently, 9 months later, he developed a 3.2 cm left submandibular mass followed by recurrence of the left gingival mass. From the clinicopathologic perspective, this had to be separated from the differentials: ganglioneuroblastoma or metastatic involvement of a lymph node from primary gingival undifferentiated carcinoma.

Key words: Collision tumor, ganglioneuroma, metastatic undifferentiated carcinoma

INTRODUCTION

Ganglioneuromas are an intriguing group of neural tumors most commonly located in the posterior mediastinum, retroperitoneum, pelvic and sacral sympathetic ganglia with rare locations in the heart, bone, spermatic cord, middle ear, orbit and skin.[1,2] The occurrence of ganglioneuroma in the neck region is limited to approximately six cases in the English literature [Table 1].[3-8] Herein, we describe a rare finding of a left submandibular mass presenting with a collision tumor consisting of cervical ganglioneuroma and metastatic tumor from the primary gingival undifferentiated carcinoma.

CASE REPORT

A 53-year-old man presented with a 2 × 1.5 × 0.7 cm left gingival mass to an outside hospital where excision of the mass was performed with a diagnosis of non-Hodgkin lymphoma. The patient had received a regimen of systemic chemotherapy inclusive of six cycles of a combination of cyclophosphamide, adriamycin, vincristine and prednisone. The patient presented at our institution for a consult and review of the pathology. According to the outside report, macroscopy of the primary gingival mass showed a tan-white to gray, soft, smooth and homogeneous cut-surface. Only H&E stained sections were available for microscopic evaluation revealing atypical and malignant cells arranged in sheets, cords, nests and trabeculated patterns. The cells were pleomorphic with a partly vesicular chromatin and prominent nucleolus. The surface squamous epithelium was focally ulcerated. Due to the limited material available for review, the diagnosis of malignant undifferentiated neoplasm involving keratinized squamous epithelium was rendered. Nine months later, he presented with a left submandibular mass. Computed tomography (CT) showed a 3.2 × 2.5 × 2.2 cm enhancing mass in the left submandibular area with enlargement of lymph nodes in the cervical neck at levels IIa and IIb and with a radiological impression of metastatic carcinoma involving a cervical lymph node [Figure 1a]. This left submandibular mass was subsequently excised.

Grossly, the left submandibular mass was tan-white, well-circumscribed with a tan-white to yellow, smooth, soft and a centrally necrotic/cystic cut-surface. Microscopy revealed two components; an undifferentiated central epithelial component with a second component composed of ganglion and Schwann cells embedded within a neurofibrillary matrix [Figure 1b-i]. Immunohistochemical staining of the metastatic undifferentiated component within the left submandibular mass demonstrated diffuse staining for CK-AE1/AE3, CK8/18, S-100 protein and focal positivity for CD56. The undifferentiated tumor cells, in the submandibular mass, were negative for synaptophysin, chromogranin, neuron-specific enolase, melan-A, glial fibrillary acidic protein (GFAP), CD45, CD99, CD20, cytokeratin (CK) 5/6,

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Table 1:Clinicopathologic features of cervical ganglioneuromas in the literature

Case/series	Age/gender	Size (cm)	Side and location	Treatment	Follow-up (months)
Mahajan *et al*., (2013)[3]	7/M	7.0	Left neck	Excision	NS
Kolte (2011)[4]	8/F	5.0	Left lateral neck	Excision	NS
Califano *et al*., (2001)[5]	11/F	2.0	Left suprahyoid region	Excision	NED (6)
Leonardis *et al.* (2003)[6]	50/M	10.0	Adjacent to left thyroid lobe	Excision	NS
McFarland and Sappington (1935)[7]	7/F	6.0 and 5.0	Right neck	Excision	NED (24)
Yokoi *et al*., (2012)[8]	19/F	7.2	Mid-Pharynx	Excision	NED (60)
Present case	53/M	4.0	Left submandibular region	Excision	NED (10)

NS=Not specified, NED=No evidence of disease, M=Male, F=Female

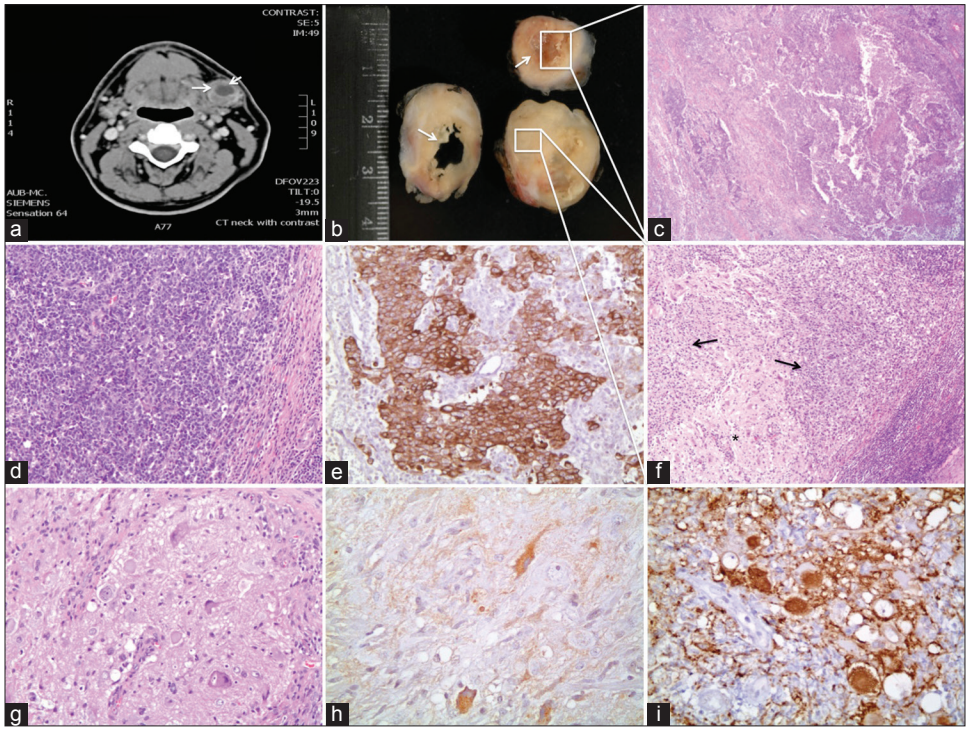

Figure 1: Cervical ganglioneuroma in collision with a metastatic undifferentiated carcinoma. (a) CT head and neck region showing a 3.2 cm mass (arrows) characterized by a central low-signal intensity area suggestive of cystic degeneration. (b) Gross photograph of the left submandibular mass revealing a centrally necrotic and cystic area (arrows). (c and d): Central necrotic area is composed of primitive malignant epithelial cells (H&E stain, (c) ×40 and (d) ×200). (e) The central tumor cells expressing cytokeratin AE1/AE3 (IHC stain, x200). (f) The peripheral region of the mass contained areas of both primitive malignant cells (arrows) in close association with the ganglioneuronal component (asterisk) (H&E stain, ×100). (g) Ganglion and Schwann cells constituted the ganglioneuronal component (H&E stain, x400). (h) The ganglion and Schwann cells show granular expression of chromogranin (IHC stain, x400). (i) Expression of synaptophysin within the ganglion cells (IHC stain, x400)

CK7, CK20, epithelial membrane antigen (EMA), p63 and Epstein-Barr virus (EBV) surface antigen. Chromogranin and synaptophysin were positive in the ganglion cells of the neural component. Due to the discrepancy between the outside diagnosis of the primary gingival mass and the current left submandibular mass, tissue material on the primary gingival mass was requested. The latter demonstrated a morphology and immunohistochemical staining pattern similar to the undifferentiated epithelial component within the left submandibular mass. Based on the aforementioned findings, the case was best interpreted as a collision tumor between a cervical ganglioneuroma and a metastatic undifferentiated carcinoma from a primary gingival lesion. Two months postoperatively, the patient presented with an induration at the previous excision site of the gingival mass with a positive uptake on positron emission tomography (PET). Microscopy demonstrated involvement of the tooth enamel base by an undifferentiated carcinoma [Figure 2]. The patient subsequently underwent partial left hemimandibulectomy. The residual tumor was grossly and microscopically involving the mandible and was focally in contact with the overlying superficial gingival squamous epithelium. There was associated focal dysplasia in the overlying squamous epithelium [Figure 3]. The patient is alive and well with no evidence of disease, 10 months postoperatively.

DISCUSSION

Tumors originating from nerve tissue were initially termed "neuroma" as described by Odier in 1803[9] with an origin

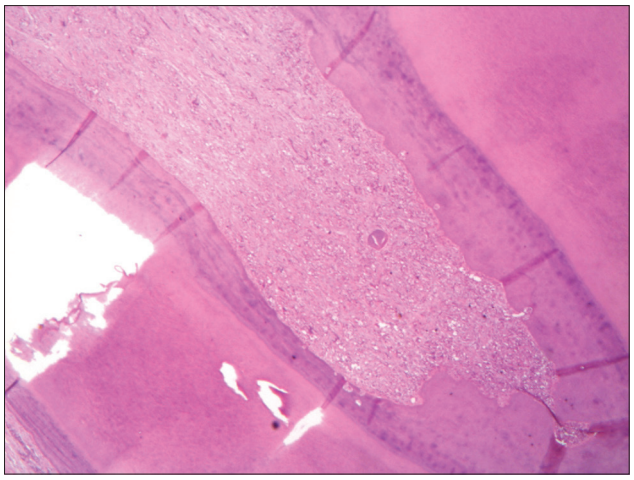

Figure 2: Tooth enamel base and gingiva involved by an undifferentiated carcinoma (H&E stain, x40)

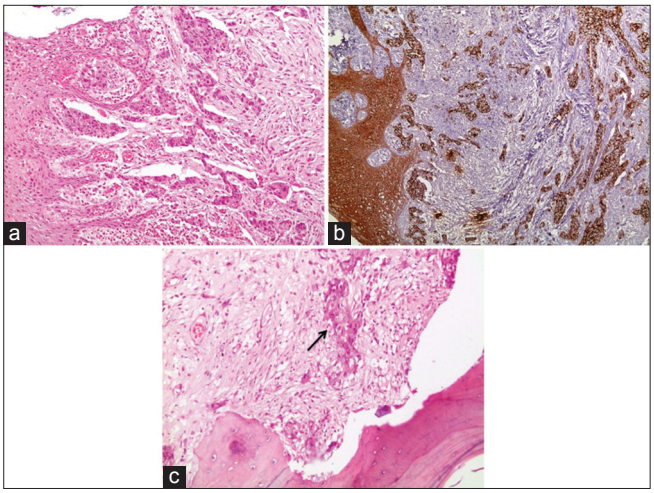

Figure 3: (a) Primary gingival undifferentiated carcinoma focally in contact with the overlying squamous epithelium (H&E stain, x200). (b) The cells diffusely expressing cytokeratin AE1/AE3 (IHC stain, x100). (c) The malignant epithelial clusters invading the underlying mandibular bone (arrow) (H&E stain, x400)

attributed to the sympathetic ganglia by Gunsbury[7] followed by a histologic rather than clinical description by Virchow in 1863.[10] Cervical ganglioneuromas are extremely rare with the majority of reported cases occurring in the pediatric age group [Table 1].

Surgical excision of ganglioneuromas is curative and recurrences are a rare and unlikely event. Considering the complex morphological features in this case, ganglioneuroblastoma was considered in the differential diagnosis. This tumor usually contains an undifferentiated component, which stains positively for neural markers. However, the tumor had both ganglion and Schwann cells embedded within a mature neurofibrillary background and associated with an undifferentiated highly malignant epithelial component expressing CK (CKAE1/AE3) staining. Such features are not representative of ganglioneuroblastoma.

The clinical presentation in addition to the imaging studies was highly suspicious of a lymph node metastasis from the primary gingival undifferentiated carcinoma. Furthermore, a small rim of a mixed inflammatory lymphoid infiltrate surrounding the lesion, assumed to be reactive in nature, raised the possibility of a cervical lymph node metastasis. There was no evidence of any residual lymphoid follicles and CD20(+) B-cells were scattered focally constituting the minority of lymphoid cells. Despite a surrounding pseudocapsule, no remnant subcapsular sinus histologically suggestive of a lymph node was identified. The presence of two distinct components consisting of undifferentiated epithelial cells and a well-differentiated ganglioneuronal element supports the entertained diagnosis of a cervical ganglioneuroma collision with a metastatic undifferentiated carcinoma.

Alternative differential diagnoses inclusive to the nasal and oral cavity encompass small cell neuroendocrine carcinoma, neuroblastoma, rarely primitive neuroectodermal tumor (PNET)/Ewing sarcoma and malignant melanoma. Although the primary gingival tumor is CKAE1/AE3 positive, neural markers were mostly negative; thus excluding a small cell neuroendocrine carcinoma. Neuroblastoma expresses S-100 protein and neural markers. PNET/Ewing sarcoma demonstrates in the majority of cases positive staining for CD99 while malignant melanoma usually expresses melanin markers such as HMB-45 and melan-A. Merkel cell carcinoma was also considered as a differential; synaptophysin and chromogranin were both negative in the primary gingival and submandibular mass. Sarcomatoid carcinoma with divergent differentiation is excluded based on the absence of spindle cells, polypoid squamoid cells and negative p63 staining. The undifferentiated round cell morphology with CK staining essentially dismisses the differential of a malignant peripheral nerve sheath tumor.

One consideration in the pathogenesis of this unusual pathological picture is the possibility of a primary neuroblastoma or PNET/Ewing sarcoma that has undergone neural-like differentiation secondary to chemotherapy following metastasis to a cervical lymph node.[11-13] However, the primary tumor lacked expression of neural markers or CD99 except for S-100 protein. The significance of S-100 protein expression is unknown; staining for S-100 protein is recognized to be nonspecific and may be observed in a variety of tumors of neuroectodermal origin. Finally, a hematolymphoid malignancy was excluded based on the negative CD45 and CD20. The striking strong and diffuse CK expression is highly in favor of a carcinoma. The epithelial origin, although EMA was negative,[14] is also supported by the focal dysplasia observed in continuity with the invasive undifferentiated carcinoma, as noted on the left hemimandibulectomy resection specimen. EBV staining

for latent membrane antigen (LMP) was done in order to determine whether EBV is associated with the lesion. In fact, Kamel *et al*.,[15] reported a 38% correlation between EBV and head neck squamous cell carcinomas, while other reports showed a rare association.[16] The clinical relevance of a collision tumor versus a unifying lesion is reflected by the tumor stage, whereby upstaging of the tumor occurs if one considers lymph node metastasis as the mechanism of tumor spread. Therefore, close follow-up with serial PET scans and alternative-imaging modalities is indicated.

CONCLUSION

A rare case of a collision tumor presenting in the left submandibular region composed of a metastatic primary gingival undifferentiated carcinoma and cervical ganglioneuroma is described. The rarity of both presentations renders the current case extremely unique. Although rare, clinically one should consider the differential diagnosis of a collision tumor even in cases where there is high suspicion of lymph node metastasis.

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