Case Report

Small cell neuroendocrine carcinoma of the paranasal sinus with intraoral involvement: Report of a rare case and review of the literature

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Abstract

The diffuse neuroendocrine system continues to be an enigmatic topic of study in pathology due to its controversial embryologic origins, biology and a variety of tumors engendered. Originally thought to be localized to the classic neuroendocrine organs (pituitary, thyroid, pancreas and adrenal medulla), the neuroendocrine cells are now known to be distributed in every organ system of the body. A number of human diseases have been linked to aberrations in the functioning of the neuroendocrine cells. Neoplasms of the neuroendocrine system can thus occur in myriad primary sites and range in behavior from benign to lethal. Small cell neuroendocrine carcinoma (SNEC) is a high-grade neuroendocrine tumor, rarely presenting in the sinonasal region. This article reports a case of a 68-year-old male patient with primary paranasal SNEC showing intraoral involvement. The diagnosis is based on a thorough clinical, histopathological and immunohistochemical workup to differentiate it from the other small round blue cell tumors.

Keywords: Neuroendocrine tumors, small cell neuroendocrine carcinoma, small round blue cell tumors

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INTRODUCTION

The neuroendocrine system includes neurons and endocrine cells sharing a common phenotypic program.[1] Initially, considered to be the constitutive cells of the classic neuroendocrine organs (pituitary, thyroid, pancreas and adrenal medulla), the neuroendocrine cells are now known to be present in every organ of the body and referred to as the diffuse neuroendocrine system (DNES).[2]

Neoplasms of the neuroendocrine system are epithelial neoplasms with predominant neuroendocrine differentiation and constitute a rare and heterogeneous group of neoplasms which can occur in myriad sites and characterized by embryological, biologic and histopathological differences, referred to as the "neuroendocrine tumors" (NETs) [Figure 1].[3] Currently, there is no system of nomenclature, grading, or staging for neuroendocrine neoplasms that is common to all anatomic sites. Morphologically similar NETs differ in the terminology and criteria adopted for histologic grading and staging depending on the site of origin.[3] Small cell neuroendocrine carcinoma (SNEC) is a high-grade neoplasm, characterized by proliferation in sheets, cords, or ribbons of small-to-oval cells with hyperchromatic nuclei, sparse cytoplasm and high nuclear/cytoplasmic ratio.[4] The present case of SNEC of the paranasal sinuses was

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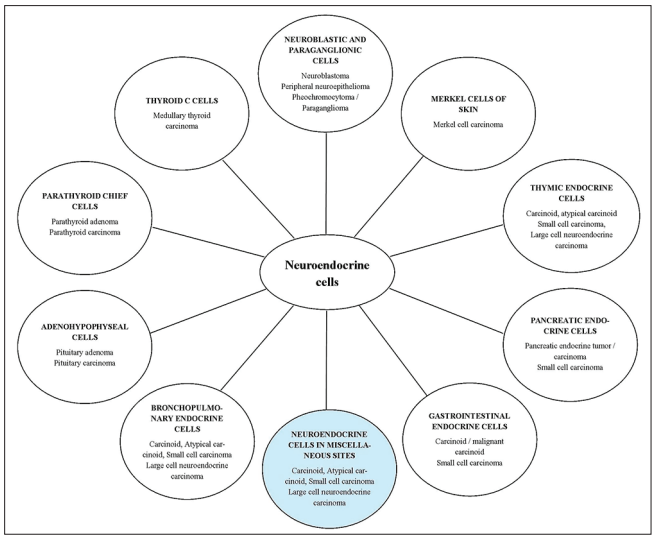

Figure 1: Spectrum of neuroendocrine cells and associated tumors

diagnosed using immunohistochemistry after distinguishing it from the other small round blue cell tumors.

CASE REPORT

A 68-year-old male patient reported to the Department of Oral and Maxillofacial Pathology with a chief complaint of swelling over the right infraorbital malar region since 20 days. The swelling measured 5 cm × 3 cm in greatest dimensions, intraorally obliterating the upper right buccal vestibule. Right submandibular lymph nodes were palpable and tender. Incisional biopsy of the lesion was performed. Light microscopic examination of the biopsy specimen revealed a homogenous mass of proliferating small, round cells with scanty cytoplasm and hyperchromatic nuclei; few cells showed evidence of nuclear molding. Areas of tissue necrosis and crush artifact were evident [Figure 2]. Tumor cells showed positivity for cytokeratin, chromogranin, synaptophysin and thyroid transcriptional factor-1 whereas negativity for CD45, CD56 and carcinoembryonic antigen [Figure 3]. The patient was thus diagnosed as SNEC, stage D (Morita Modification of the Kadish Staging System) with a grade IV (Hyam's Grading System).

DISCUSSION

The DNES based on its derivation comprises two distinct groups.

a. Neural crest origin (adrenal medullary cells, melanocytes, paraganglia, sympathetic ganglia, thyroid-C cells)
b. Neuroendocrine-programmed origin (gastrointestinal, hepatobiliary, lower and upper respiratory tracts, sinonasal tract, pancreatic endocrine cells, parathyroid cells).[5,6]

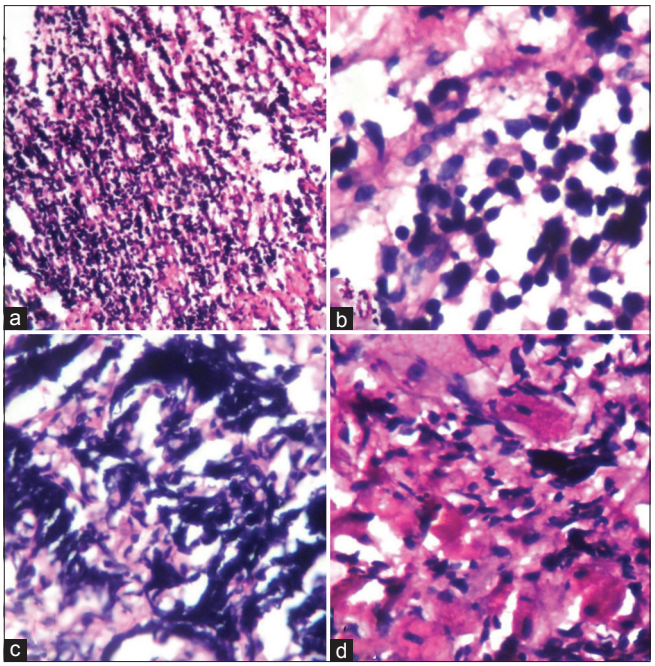

Figure 2: Photomicrograph of small cell neuroendocrine carcinoma showing the presence of (a) uniform population of small round cells (×400), (b) Nuclear molding (×400), (c) Crush artifact (×100), (d) Invasion and destruction of soft tissues (×100)

The neonatal respiratory tract contains a prominent system of neuroendocrine cells; both dispersed and aggregated into neuroepithelial bodies. Both types decline numerically during childhood. In adults, clusters of these cells are situated in the basal layers of the respiratory epithelium.[7]

The sinonasal tract refers to the paranasal sinuses (maxillary, ethmoid, sphenoid and frontal) and the nasal cavity which is lined by ectodermally derived respiratory (Schneiderian) mucosa, consisting of pseudostratified columnar-ciliated epithelium with interspersed goblet cells and neuroendocrine cells.[6]

Neuroendocrine cells are conventionally described as cells lacking axons and synapses and:

1. Possessing the ability to produce neurotransmitters, neuromodulators, neuropeptide hormones, or neuropeptide processing enzymes (subtilase-like proprotein convertases)
2. Containing dense core secretory granules containing a variety of substances (such as fluorogenic amines, aromatic amino acid decarboxylase nonspecific esterases and/or cholinesterases and others).[8]

However, neuroendocrine cells can no longer be defined simply based on their synthesis/content of neuropeptides or chromogranins.[9] When appropriately stimulated, cells of diverse embryologic origins that are neither neural nor endocrine can acquire at least

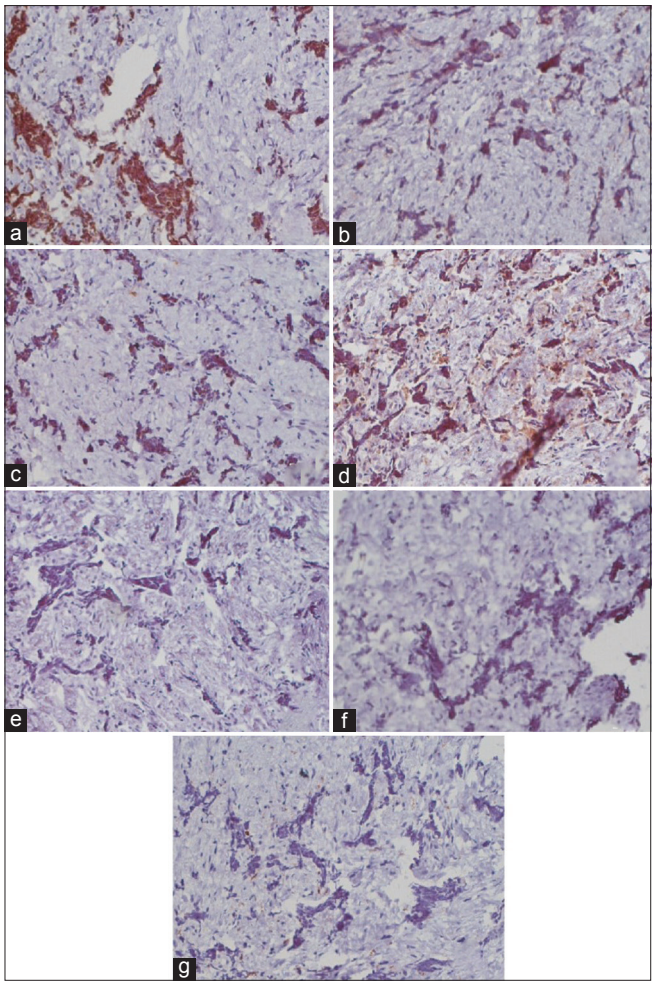

Figure 3: Immunohistochemical analysis of various markers in the tumor mass. (a) Thyroid transcription factor 1+ (b) Synaptophysin+, (c) Cytokeratin 20+, (d) Chromogranin+, (e) Carcinoembryonic antigen−, (f) CD56−, (g) CD45− (×100)

partial neuroendocrine phenotype characteristics that are ascribed to the neuroendocrine cells, including the expression of the various substances mentioned above.[10] This morphological and functional plasticity under the control of hitherto unelucidated genetic switches might help explain many of the apparently aberrant characteristics of neuroendocrine cells under pathological conditions.[8]

Heidenhain (1870) described scattered cells throughout the intestinal mucosa, structurally and functionally different from other cells of the mucosa that showed reactivity for chromium and silver salts.[10,11] Nicholas (Nikolai) Kultschitzky (1897) in his paper "Zur Frage über den Ban des Darmkanals" mentioned that unlike the mucous-secreting and absorbing cells of the intestinal mucosa, these cells emptied their secretory products toward the basilar pole of the mucosa and possibly into the vessels.[11]

Masson (1914) demonstrated argentaffin positivity in these cells.[10] Later studies demonstrated that these cells with similar histochemical properties were not restricted to the intestinal mucosa but were diffusely distributed in the body. They were identified in the bronchopulmonary tract, thymus, thyroid gland, skin, pancreatic islets, parathyroid glands, endocrine cells of the breast and the genitourinary tract.[10,12,13]

These cells were recognized independently by several other investigators and were given different terminologies, such as "enterochromaffin cells," "argentaffin cells," "clear cells," "enteroendocrine cells," "Kultschitzky cells," and "paraneurons."[9,11]

In 1938, Feyrter identified the Helle Zellen cells (clear cells) and grouped these endocrine cells located in various organs and dispersed throughout the body into the DNES.[14] Due to his extensive work in this field, he has been referred to as the "Father of Neuroendocrinology."[14] With the detection of similar biogenic amines and peptide hormones in neurons and in the dispersed endocrine system, Pearse (1966) developed the amine precursor uptake and decarboxylation (APUD) concept.[8]

The term "APUD cell" has fallen into disuse because embryological studies have conclusively demonstrated that neither all neuroendocrine cells have amine-synthesizing ability nor are all cells with neuroendocrine characteristics derived from the neuroectoderm.[8,9] The current concept of a neuroendocrine cell does not support a neuroectodermal origin.[9] The term "neuroendocrine" is used to denote the shared phenotype characterized by the expression of the endocrine and neural features and highlights one of the important facts in biology that the developmental regulation of genetic expression is not necessarily related to cell lineage.[10] The neuroendocrine-programmed cell is therefore identified by cell markers expressed by different genes ranging from cell surface markers, constituents of secretory granule matrix and membranes, hormone-synthesizing enzymes, enzymes related to cellular energy metabolism and cytoskeletal elements.[6,8]

Cell identity is defined by molecular properties and phenotypic characteristics linked to germ layer derivation. As markers not associated with neuroendocrine cells have been detected within tumors of neuroendocrine origin, it follows that the genetic switches that control the expression of neuroendocrine markers, viz., neuropeptides/chromogranin by tumor cells, have been turned on resulting in the acquisition of a neuroendocrine phenotype rather than being of true embryonic neuroectodermal origin.[8]

The general function of the neuroendocrine system is in maintaining homeostasis.[9,11,15] The neuroendocrine cells of the respiratory tract exert multiple effects on airway function which include contraction of airway smooth muscle; mucus secretion; vasodilation and plasma extravasation; stimulation of mast cells, macrophages, lymphocytes, eosinophils, chemotaxis and vascular adhesion of neutrophils.[7,15] Neuroendocrine cells may also play a role in stimulation of growth of sensory and sympathetic nerves in addition to its role in stimulating the sensory nerves to release neuropeptides.[9,11,15]

Specific causes of altered neuroendocrine function are still not fully elucidated. Neuroendocrine dysfunction may manifest as temperature lability, disturbances in appetite, weight fluctuations, hypothalamic disorders, pituitary disorders, disorders of fluid regulation, hypertension or hypotension, fatigue, increased anxiety, depression, memory failure, cognitive deficiencies, reduced bone and muscle mass and immunologic disorders and has been associated with various chronic diseases.[16]

Tumors arising from the neuroendocrine cells or the neoplasms showing prominent neuroendocrine differentiation constitute a heterogeneous group of epithelial neoplasms referred to as the NETs.[16]

Neuroendocrine neoplasms or NETs are classified into well differentiated (typical), moderately differentiated (atypical carcinoids) and poorly differentiated (small and nonsmall cell types). Well and to a lesser extent, moderately differentiated NETs tend to carry better prognosis with low metastatic rates and better survival, while poorly differentiated NEC (SNECs) are characterized by rapid growth and fatal outcome prognosis. Treatment recommendations for this entity vary considerably largely due to a lack of consensus and variable pathological classifications.[17]

Literature reveals multiple site-specific systems of nomenclature and classification. In the absence of a classification system for NETs involving the sinonasal tract, the classification scheme of the laryngeal NECs has been extended to the sinonasal NETs.[18,19]

Differentiation is the extent to which a neoplasm recapitulates the features of the nonneoplastic cellular components, whereas grade refers to the inherent biological aggressiveness of a neoplasm.[16] The grade of NETs is a fundamental predictor of outcome, and grading parameters are part of the most classification systems [Table 1].[3,16,18] Thus, the well-differentiated NECs (G1/G2 NETs) retain the morphological similarities with nonneoplastic neuroendocrine cells, grow in nesting, trabecular and organoid forms and express markers of neuroendocrine differentiation; mitosis and necrosis are infrequent. However, the poorly differentiated (G3 NETs) bears little resemblance to normal neuroendocrine cells, grow in less organized pattern, with frequent necrosis and mitosis.[16]

Although there is a standardized grading system (European NET Society [ENETS]/WHO grading system) for the NETs for the gastroenteropancreatic system, no such system has been developed for the sinonasal NETs due to the rarity of such lesions in the sinonasal tract.[16,19] And as such, the Hyam's Grading System which was originally devised for esthesioneuroblastoma has been extrapolated to the sinonasal NETs [Table 2].[20]

Although the ENETS and American Joint Committee on Cancer (AJCC) staging systems have been prognostically

Table 1: Classification systems of neuroendocrine tumors (European Neuroendocrine Tumor Society, gastroenteropancreatic)

Grade	Wick (2000) (all sites)	ENETS (2006-2007) (GEP)	WHO (2010) (GEP, liver)
Low	NEC, Grade 1	NETs, Grade 1	Neuroendocrine neoplasm, Grade 1
Intermediate	NEC, Grade 2	NETs, Grade 2	Neuroendocrine neoplasm, Grade 2
High	NEC, Grade 3, small cell carcinoma	NEC, Grade 3 (small cell carcinoma)	Neuroendocrine neoplasm, Grade 3, small cell carcinoma
	NEC, Grade 3, large cell NEC	NEC, Grade 3 large cell NEC	Neuroendocrine neoplasm, Grade 3, large cell NEC

NETs: Neuroendocrine tumors, NEC: Neuroendocrine carcinoma, GEP: Gastroenteropancreatic, ENETS: European Neuroendocrine Tumor Society

Table 2: Grading system for the sinonasal neuroendocrine tumors

	Hyam's grading systems for the sinonasal NETs				
	Lobular architecture	Neuropil	Rosettes	Necrosis	Nuclear Pleomorphism
Grade I	++	++	+/-	-	-
Grade II	+	+	+/-	-	+
Grade III	-	+/-	+/-	+	++
Grade IV	-	-	-	++	+++

NETs: Neuroendocrine tumors, -: Absent, +/-: May or may not be present, +: Present, ++: Prominent, +++: Marked

used to stage tumors of the gastrointestinal and pancreatic NETs, it cannot be applied to the sinonasal NETs.[16] The Kadish system, Morita Modification of the Kadish Staging System and the 2009 AJCC system for nasal cavity and paranasal sinus tumors have been commonly applied to the sinonasal NETs [Table 3].[19-21]

SNEC is a poorly differentiated NET. Within the head and neck region, NEC most commonly occurs in the larynx, followed by the salivary glands and sinonasal region.[4] Paranasal NEC is rare and accounts for approximately 5% of malignancies of this site, with maxillary sinus being the most frequently involved paranasal sinus (60%).[22,23] Head and neck SNECs show a slight male predominance.[24]

The clinical features are nonspecific similar to other sinonasal tumors and could be grouped into rhinological symptoms, ophthalmic signs and other signs suggestive of locoregional invasion.[24,25] Nasal obstruction, rhinorrhea and epistaxis are the common rhinological symptoms. The ophthalmic signs include exophthalmos, loss of visual acuity and limitation of eye mobility.[25]

Because of the thin bony partitions between the nasal cavity, sinuses, orbit and cranial vault, invasion into the adjacent structures is common.[24] Locoregional invasion can be suspected in the presence of local pain, anosmia, or any tender swelling over the nose or paranasal sinuses.[25]

Paraneoplastic syndromes due to ectopic hormone production also occur.[24] However, clinical evidence of endocrine overactivity in the head and neck tumors is rarely detected.[26] Kameya *et al*. have reported cases with increased levels of adrenocorticotrophic hormone and calcitonin.[27]

Metastasis to the lungs, liver and bone is fairly common.[28] Metastatic cervical lymph nodes have also been described.[22,25] As the tumor can metastasize to different sites, diagnosis of secondary small cell carcinoma should

Table 3: Staging systems for the sinonasal neuroendocrine tumors

Morita modification of Kadish staging	AJCC cancer staging manual (7th edition, 2009)								
	T classification			N classification		M classification		Staging	
		Maxillary sinus	Nasal cavity and ethmoid sinus						
Stage A: Tumor involving nasal cavity	Tis	Carcinoma in situ	Carcinoma in situ	NX	Regional lymph nodes cannot be assessed	M0	No distant metastasis	Stage 0	TisN0M0
Stage B: Tumor involving paranasal sinuses	T1	Tumor limited to the mucosal lining	Tumor limited to the mucosal lining at one subsite	N0	No regional lymph node metastasis	M1	Distant metastasis	Stage I	T1N0M0
Stage C: Tumor extending beyond nasal and paranasal sinuses	T2	Bone erosion or destruction limited to the hard palate and middle meatus	Tumor at two subsites or adjacent nasoethmoid site	N1	Metastasis in a single ipsilateral lymph node, ≤3 cm in greatest dimension			Stage II	T2N0M0
Stage D (Morita modification): Tumor metastatic to cervical lymph nodes or distant metastasis	T3	Bone erosion or destruction of the posterior bone of maxillary sinus, floor and medial bone of orbit. Tumor growth into the pterygoid fossa or ethmoid sinus	Bone erosion of lamina papyracea or floor of orbit, maxillary sinus, palate and, cribriform plate	N2	Metastasis in a single ipsilateral lymph node, >3 cm but ≤6 cm in greatest dimension, or metastases in multiple ipsilateral lymph nodes, ≤6 cm in greatest dimension, or in bilateral or contralateral lymph nodes, ≤6 cm in greatest dimension			Stage III	T3N0M0, T1-3N1M0
	T4a	Tumor growth into the anterior orbit, pterygoid plates, infratemporal fossa, cribriform plate, frontal sinus, sphenoid sinus, or skin of cheek	Tumor growth into the anterior orbit, anterior cranial fossa, pterygoid plates, frontal sinus, sphenoid sinus, or skin of nose or cheek	N2a	Metastasis in a single ipsilateral lymph node, >3 cm but ≤6 cm in greatest dimension			Stage IVA	T4aM0N0 or T1-4aN2M0
	T4b	Tumor growth into the orbital apex, dura, brain, middle cranial fossa, cranial nerves other than V2, nasopharynx and clivus		N2b	Metastases in multiple ipsilateral lymph nodes, ≤6 cm in greatest dimension			Stage IVB	T4bN0M0 or AnyTN3M0
				N2c	Metastases in bilateral or contralateral lymph nodes, ≤6 cm in greatest dimension			Stage IVC	AnyTAnyNM1
				N3	Metastasis in a lymph node, >6 cm in greatest dimension				

AJCC: American Joint Committee on Cancer

Table 4: Histopathological features of small round blue cell tumors

Cell lineage	Tumor	Distribution	Nuclear features	Mitotic figures	Anaplasia	Necrosis	Other features
Epithelial/ neuroectodermal	SNEC	Ribbons, islands, sheets, cords and ribbons	High nuclear/ cytoplasmic ratio, nuclear molding. The nuclei are oval to pleomorphic with absent or indistinct nucleoli	High	Variable	Prominent necrosis, varies from scattered, individual necrotic cells to confluent ("geographic") areas of necrosis	Characteristic "crush artifact" and "Azzopardi effect" (smudged hematoxylinophilic deposits-DNA encrustation) in vascular walls Glomeruloid vascular proliferation
	SNUC	Sheets and nests, wide trabeculae or ribbons	Large ovoid nuclei with inconspicuous to prominent nucleoli	High	Common	Individual cell necrosis and central comedo-type necrosis	Distinct cytoplasmic borders, vascular invasion is extensive
	NK-SSC	Syncytium	Hyperchromatic nuclei, prominent nucleoli	Variable	Common	Limited	-
	ONB	Lobular, solid, nests or sheets	Hyperchromatic small round nuclei, punctate chromatin and absent or small nucleoli	Variable	Variable	Variable	Presence of a fibrillary cytoplasmic background, Flexner-type or Homer-Wright-type rosettes, rarely ganglion cells
	MM	Solid, fascicular and peritheliomatous, nesting or theque-like pattern	Hyperchromatic nuclei with prominent nucleoli	Present	Common	Common	Tumor giant cells (50% of the cases) and melanin pigment (75%of the cases)
	ES	Sheets, lobules or nests	Round hyperchromatic nuclei, with inconspicuous to small nucleoli	Present	Infrequent	Variable/common	Indistinct cytoplasmic borders Homer-Wright rosettes, with centrally located fibrillary material may be present Intracytoplasmic glycogen Periodic Acid Schiff diastase resistant staining
	LE CA	Islands, sheets, syncytial growth. Regaud pattern-cohesive nests and cords that are demarcated sharply from the surrounding inflammation Schmincke pattern-tumor cells arranged diffusely as single cells and small nests permeated by the inflammatory infiltrate	Vesicular to hyperchromatic, round to oval nuclei and prominent eosinophilic nucleoli	Numerous	Present	Focal to absent	Distinctive morphologic feature is the presence of a dense, nonneoplastic inflammatory infiltrate, which consists primarily of lymphocytes and plasma cells
Hematopoietic	Extranodal NK/T cell LYM	Diffuse neoplastic lymphoid proliferation	Hyperchromatic	Frequent	Common	Common	Vascular invasion/ destruction and pseudoepitheliomatous hyperplasia Demonstration of the EBV virus (present in nearly all cases)
	PCT	Sheets	Large nucleus with an increased nuclear/ cytoplasmic ratio, coarse nuclear chromatin and prominent nucleoli	Variable	Occasional	Uncommon	Diffuse infiltrate of uniform (well-differentiated) to pleomorphic (anaplastic) neoplastic plasma cells Amyloid deposits (11-38% of the cases)

Contd...

Table 4: Contd...

Cell lineage	Tumor	Distribution	Nuclear features	Mitotic figures	Anaplasia	Necrosis	Other features
Mesenchymal	RMS	Sheets Alternating hypercellular and hypocellular areas	Nuclei are small, round, or oval, small nucleoli	Variable	Common	Limited	Subepithelial linear band of more compactly arranged neoplastic cells characteristic of the botryoid variant-common in the sinonasal region Identification of 'strap cells'
	Poorly differentiated SS	Nests or cords	Hyperchromatic nuclei	Variable	Infrequent	Variable	May show a typical biphasic or monophasic pattern. Other poorly differentiated forms include large (epithelioid) cell and high-grade spindle cells

SNEC: Small cell neuroendocrine carcinoma, SNUC: Sinonasal undifferentiated carcinoma, NK-SCC: Nonkeratinizing squamous cell carcinoma, ONB: Olfactory neuroblastoma, MM: Multiple myeloma, ES: Ewing's sarcoma, LE CA: Lymphoepithelial carcinoma, NK/T cell LYM: Natural killer/T cell lymphoma, PCT: Plasmacytoma, RMS: Rhabdomyosarcoma, SS: Synovial sarcoma, EBV: Epstein-Barr virus

be kept in mind.[29] Majority of the patients present with an advanced stage tumor.[19]

Poorly differentiated NEC or SNEC consists of sheets, cords and ribbons of small- or intermediate-sized cells with poorly defined cell borders.[24,26] Nuclei are round to oval and contain dense or finely granular delicate chromatin.[24,26,30] It may have scanty or moderate eosinophilic or amphophilic cytoplasm.[24,26] Mitotic figures and areas of necrosis are frequent. Necrosis varies from scattered, individual necrotic cells to confluent "geographic" areas of necrosis producing the "crush artifact."[26,31] The "Azzopardi effect" (smudged hematoxylinophilic deposits in blood vessel walls) may be present.[32] Lymphatic, perineural and soft tissue invasion is common.[19,26,33]

Immunohistochemical markers of neuroendocrine differentiation include neuron-specific enolase (protein 14-3-2), protein gene product 9.5 (PGP9.5), chromogranins, secretogranins, secretory granule proteins, synaptic vesicle protein 2 and neural cell adhesion molecules.[10] Electron microscopy shows limited neuroendocrine differentiation in the form of sparse membrane-bound dense core neurosecretory granules; tonofilaments may be present occasionally. Cell junctions are absent but could show the presence of well-formed desmosomes.[31]

Paucity of randomized studies on these uncommon tumors has led to a lack of consensus on the management protocol.[34] Chang *et al*., Qian *et al*. and Likhacheva *et al*. have suggested that combined treatment strategy based on surgery has a better disease-free survival and overall survival as compared to treatment without surgery, irrespective of differentiation status of the tumor.[35-37] Somatostatin analogues and immunotherapeutic agents (interferon alpha) have been recently introduced for the systemic treatment of disseminated disease.[38]

The sinonasal SNEC represents the poorly differentiated form of NET and needs to be differentiated from a group of neoplasms referred to as the "small round blue cell tumors" of the sinonasal area.[39] It is a group of undifferentiated neoplasms showing little or no evidence of differentiation that share the common light microscopic appearance of being composed of relatively small, round to round-spindled, monotonous cells.[31,32]

Final diagnosis of such neoplasms rests on the immunohistochemical evaluation as well as on genetic analysis.[31,32,40] Such an undifferentiated tumor could either represent a metastasis of unknown origin or a primary neoplasia without obvious cell line of differentiation exhibiting pleomorphic to anaplastic appearance.[40] They lack any particular morphologic features that make diagnosis solely based on light microscopic examination difficult.[32]

However, minor differences between the different tumors encompassing the group are provided in Table 4.[31,39,41,42]

From a therapeutic point of view, it is critical to determine whether an undifferentiated neoplasm is epithelial, mesenchymal, or hematopoietic; and as such, a broad lineage differentiation of an undifferentiated tumor is important. Bahrami provided a practical algorithmic approach for the immunohistochemical dissection of such tumors.[40]

Table 5: Immunohistochemical and cytogenetic features of small round blue cell tumors

	SNEC	SNUC	NK-SSC	ONB	MM	ES/PNET	LE CA	Extranodal NK/T cell LYM	PCT	RMS	SS
CK	Positive (punctate perinuclear)	Positive	Positive	Variable	Variable	Variable	Positive	Negative	Variable	Variable	Variable
NSE	Positive	Positive	Negative	Positive	Negative	Variable	-	Negative	-	Variable	-
CG	Positive	Variable	Negative	Variable	Negative	Negative	-	Negative	-	Negative	-
SYN	Positive	Variable	Negative	Positive	Negative	Variable	Negative	Negative	-	Negative	-
S 100	Negative	Variable	Negative	Positive (periphery of the nests)	Positive	Variable	-	Negative	-	Variable	Variable
HMB	Negative	Negative	Negative	Negative	Positive	Negative	-	Negative	-	Negative	-
LCA	Negative	Negative	Negative	Negative	Negative	Negative	-	Variable	-	Negative	-
CD56	Negative	Negative	Negative	Negative	Negative	Negative	-	Positive	-	Negative	Positive
CD99	Negative	Variable	Negative	Negative	Negative	Positive	-	Variable	-	Negative	Positive
VIM	Negative	Negative	Negative	Negative	Positive	Positive	-	Variable	-	Positive	Positive
DES	Negative	Negative	Negative	Negative	Negative	Variable	-	Negative	-	Positive (diffuse)	-
MGF-4	Negative	Negative	Negative	Negative	Negative	Negative	-	Negative	-	Positive	-
Other markers	TTF-1+	EBV + leu-7/ CD57	EMA+	GFAP + (variable) Neurofibrillary protein+ β-tubulin + microtubule–associated protein + VIM+ EMA + Leu–7/ CD57+	Tyrosinase+ MART–1/ melanA+	FLI1+	EBV+ CD 45+ MNF 116+ MIB-1+ CK 5/6– CK 7– CEA– melanA– CK 20–	CD 45+ CD2+ CD3e+ CD56+ CD43+ Perforin + granzyme B+ CD3–	EMA+ light chain Immunoglobulins (either kappa or lambda)+	Myogenin+ HHF-35+ MYO D1+ Neurofilaments+ CD20+	EMA+ E-cadherin+ BCL2+ TLE1+ Calponin+ CD 34–
Cytogenetics				Gain of 13q, 20q and loss of Xp	CDKN2A/ p16 (9p21) PTEN (10q23) 1q+, 6p+, 8q+	Reciprocal trans location 11; 22 (q24;q12), which results in the fusion of the EWS gene with the FLI or ERG gene		Del (6)(q21-25) I (6)(p10) EBV (ISH) 10% of tumors with T-cell receptor gene rearra ngement, no immun oglobulin light or heavy chain rearra ngements	14q32 (IgH) (In contrast to multiple myeloma lacks the *t*(11; 14), – 13 or 13q–	ERMS Gain or loss of all or portions of chromosomes 2, 7, 8, 11, 12, 13 and/or 20 with or without loss of 22 11p15 LOH ARMS *t*(2,13) (q35;q14) PAX3-FOXO1 (50%-60%) *t*(1;13) (p36;q14) PAX7-FOXO1 (~20%) Other PAX3 variants (<1%) Fusion negative (20%-30%)	Chromosomal translocation *t*(X; 18) or the derived SYT-SSX fusion products

PNET: Primitive neuroectodermal tumor, ERMS: Embryonal rhabdomyosarcoma, ARMS: Alveolar rhabdomyosarcoma, EWS: Ewing's sarcoma, CK: Cytokeratin, NSE: Neuron specific enolase, CG: Chromogranin, SYN: Synaptophysin, HMB: Homatropine methylbromide, LCA: Leukocyte common antigen, CD: Cluster of differentiation, VIM: Vimentin, DES: Desmin, MGF: Myogenic regulatory factor, TTF-1: Thyroid transcription factor 1, EBV: Epstein-Barr virus, GFAP: Glial fibrillary acidic protein, EMA: Epithelial membrane antigen, melanA: Melanoma antigen, MART: 1: Melanoma associated antigen recognized by T cells 1, HHF-35: Common muscle actin 35, Myo D1: Myoblast determination protein1, FLI1: Friend leukemia integration factor 1, MNF 116: Pancytokeratin antibody, MIB-1: An antibody against Ki-67, CEA: Carcinoembryonic antigen, BCL-2: B-Cell lymphoma 2, TLE1: Transducin-like enhancer protein 1, CDKN2A: Cyclin-dependent kinase inhibitor 2A, PTEN: Phosphatase and tensin homolog, FOXO1: Forkhead box protein O1, PAX: Paired box homeotic, SNEC: Small cell neuroendocrine carcinoma, SNUC: Sinonasal undifferentiated carcinoma, NK-SCC: Nonkeratinizing squamous cell carcinoma, ONB: Olfactory neuroblastoma, MM: Multiple myeloma, ES: Ewing's sarcoma, LE CA: Lymphoepithelial carcinoma, NK/T cell LYM: Natural killer/T cell lymphoma, PCT: Plasmacytoma, RMS: Rhabdomyosarcoma, SS: Synovial sarcoma, ERG: ETS-related gene, ISH: In-situ hybridization, IgH: Immunoglobulin heavy chain, LOH: Loss of heterozygosity, SYT: Synovial sarcoma translocation, SSX: Synovial sarcoma X

Table 6: Algorithm for the immunohistochemical diagnosis of small round blue cell tumors

Small round blue cell tumors										
CK+					CK−					
DES−				DES+	DES−				DES+	
CD99−		CD99+		DSRCT	CD45−, S-100−			CD45+	S-100+, HMB45+	MyoG + WT1 + (cytoplasmic)	MyoG + WT1 + (nuclear)
NE markers+ SNEC	NE markers− NK-SSC	NE markers+ SNUC	NE markers− PDSS		CD99+ ES/ PNET	CD99− NE markers+ ONB	CD99− NE markers− SCOC	LYM	Malignant melanoma	RMS	Wilm's tumor

PCT: EMA+, CD138+, CD38+, CD45+, VS38+ (variable), CD79a+ (variable), CD31+ (occasional), CD56+ (occasional) LE CA: MNF 116+, EBV+, CK 5/6−, CK 7-, CEA−, melanA−, CK 20−

CK: Cytokeratin, DES: Desmin, DSRCT: Desmoplastic small round cell tumor, HMB: Homatropine methylbromide, MyoG: myogenin, WT1: Wilm's tumor: 1, LYM: Lymphoma, NE: neuroendocrine, PDSS: Poorly differentiated synovial sarcoma, SCOC: Small cell osteosarcoma, RMS: Rhabdomyosarcoma, SNEC: Small cell neuroendocrine carcinoma, SNUC: Sinonasal undifferentiated carcinoma, NK-SCC: Nonkeratinizing squamous cell carcinoma, ES/PNET: Ewing's sarcoma/ primitive neuroectodermal tumor, ONB: Olfactory neuroblastoma, EMA: Epithelial membrane antigen, CD: Cluster of differentiation, LE CA: Lymphoepithelial carcinoma, MNF 116: Pancytokeratin antibody, EBV: Epstein-Barr virus, CEA: Carcinoembryonic antigen, melanA: Melanoma antigen

It should be emphasized that each tumor requires an "individually constructed panel" composed of carefully selected antibodies that recognize all reasonable diagnostic possibilities in the context of the tumor's morphology, anatomic site and clinical/radiologic findings.[40]

A screening panel to demonstrate the expression of markers of major lineages (i.e., epithelial, mesenchymal, lymphoid and melanocytic) often provides the first clue to the nature of an undifferentiated tumor.[40]

The immunohistochemical and cytogenetic features of the small round blue cell tumors are summarized in Table 5,[31,39,43,44] and the algorithm for the immunohistochemical differential diagnosis is provided in Table 6.[39,40]

CONCLUSION

The NETs can occur in any region of the body and pose diagnostic difficulties. Knowledge of its histopathology, immunohistochemical as well as ultrastructural features can provide important clues to the diagnosis. Although recently, international consensus groups have attempted to standardize the classification, grading and staging systems of gastroenteropancreatic NETs, little progress has been made in terms of NETs of miscellaneous sites, in particular the head and neck region. In view of the increasing number of NETs in the sinonasal complex, a site-specific system of classification, staging and grading would help in the formulation of precise management protocols.

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Conflicts of interest
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