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Original Article

Esthesioneuroblastoma: an institutional based descriptive study of a rare tumor

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Esthesioneuroblatoma; Flexner-Wintersteiner; Homer Wright; Olfactory neuroblastoma; Pseudorosette; Rosette; Sinonasal tract

ABSTRACT

Background: Esthesioneuroblastoma is a slow-growing rare malignant neuroectodermal tumor arising from the olfactory epithelium. It has a bimodal incidence with peaks in the second and third decades of life and the sixth and seventh decades of life with equal incidence among men and women. Prognostic factors include the Hyams grade and modified Kadish stage. This study analyzed the clinicopathological features of esthesioneuroblastoma.

Materials and methods: Retrospective study of patients who were diagnosed with esthesioneuroblastoma at a tertiary care hospital between January 2012 and May 2019 was conducted. The research was performed according to the World Medical Association Declaration of Helsinki. Institutional research committee approval (IEC: 473/2019) was obtained.

Results: Clinicopathological profiles of 8 patients who were diagnosed with esthesioneuroblastoma during the period were included. Among the eight patients, five were female and three were male. Common presenting complaints were nasal obstruction, difficulty in breathing, epistaxis, local pain, and anosmia. The average age of presentation was 52 years, ranging from 14 to 73 years. Anterior rhinoscopic examination in these cases showed a polypoid mass located in the nasal cavity. According to the Hyams grading system, three of the eight cases were grade-2 and the remaining five cases were grade-3 Hyams histological grade. Three cases exhibited foci of ganglioneuroblastic transformation. Three patients had metastases to cervical lymph nodes and three patients had recurrence.

Conclusions: Esthesioneuroblastoma is a rare aggressive malignant tumor. It can exhibit divergent epithelial or ganglionic differentiation. A proper diagnosis should be made, graded and staged before proceeding to treatment.

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INTRODUCTION

Esthesioneuroblastoma (ENB), also called olfactory neuroblastoma is a slow-growing rare malignant neuroectodermal tumor arising from the olfactory epithelium. It is usually located in the superior nasal cavity, arising from the cribriform plate, and can have an intraorbital and intracranial extension. It was first described by Berger et al in 1924. ENB accounts for about 3–6% of all sinonasal malignancies.[1-3] It has a bimodal incidence with peaks in the second and third decades of life and the sixth and seventh decades of life with equal incidence among men and women.

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Prognostic factors include the Hyams grade and modified Kadish stage. Differential diagnoses include other small round cell tumors including neuroendocrine carcinoma, sinonasal undifferentiated carcinoma, rhabdomyosarcoma, melanoma, Ewing sarcoma, and lymphoma. ENB can exhibit divergent epithelial or ganglionic differentiation. ENB usually presents with locally aggressive disease and can metastasize widely by both hematogenous and lymphatic routes. It has a marked tendency for late local and regional recurrences.[1,4,5]

MATERIALS AND METHODS

The medical records database was searched retrospectively in a tertiary care hospital to study the clinicopathological profile of patients who were diagnosed with ENB between January 2012 and May 2019. The research was performed according to the World Medical Association Declaration of Helsinki. Institutional research committee approval (IEC: 473/2019) was taken. Detailed demographic data, clinical findings, and treatment modalities were collected. Histopathological slides were retrieved and analyzed. Microsoft Excel was used to analyze.

RESULTS

During the study period (January 2012 and May 2019), 8 patients were diagnosed with ENB. Among the eight patients, five were females and three were male (F:M= 1.67:1), The average age at presentation was 52 years, ranging from 14 to 73 years. Common presenting complaints were nasal obstruction, epistaxis, local pain, blurring of vision, and anosmia. Anterior rhinoscopic examination showed a polypoidal mass located in the nasal cavity in all cases. Two patients had intracranial extension while one had orbital involvement by the tumor. On histology, the low-grade tumor had a lobular growth pattern (fig.1) with discrete nests of small round tumor cells in a fibrillary stroma and Homer Wright pseudorosettes (fig.2).

Flexner Wintersteiner rosettes (fig.3), necrosis, and mitoses were seen in high-grade tumors. Three of the eight tumors were grade-2 and the remaining five cases were grade-3 Hyams histological grade. Three cases exhibited foci of ganglioneuroblastic transformation (fig.4). Immunohistochemistry slides were available in seven cases. All showed strong synaptophysin (fig.5) positivity in the tumor cells and S100 (fig.6) expression in the sustentacular cells. Cytokeratin, Epithelial membrane antigen (EMA), desmin, Leukocyte common antigen (LCA), and CD99 were done in a few cases to rule out other small round cell tumors

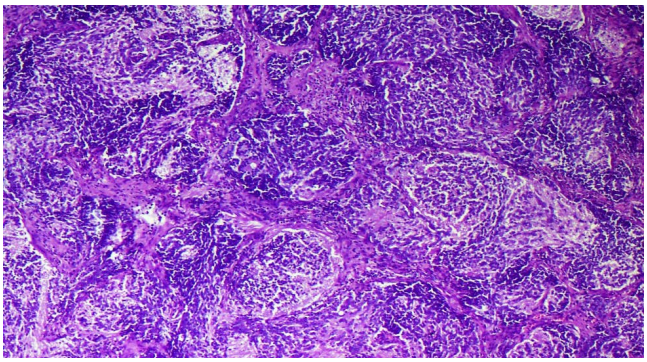

Figure 1: *Lobular architecture of tumour (HE stain; X40)*

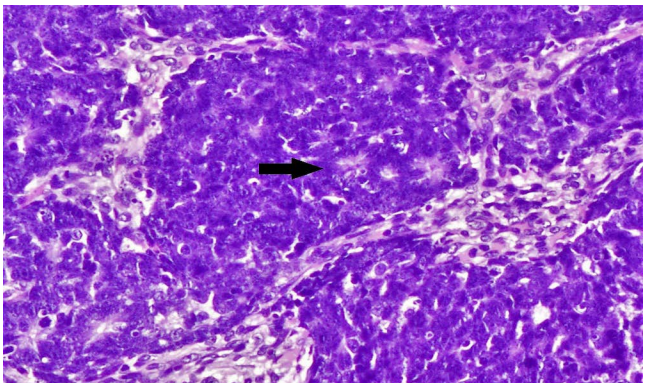

Figure 2: *Homer Wright rosette (arrow) (HE stain; X200)*

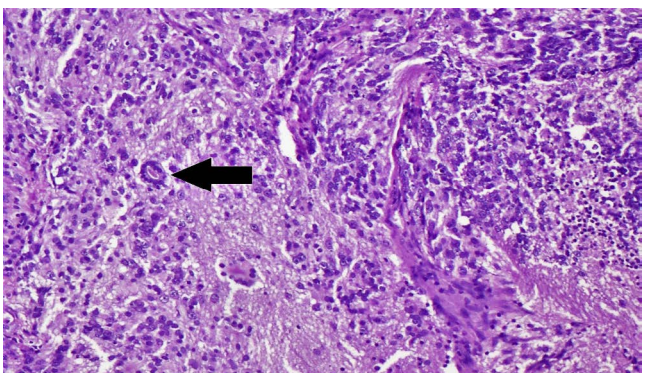

Figure 3: *Fibrillary matrix, Flexner Wintersteiner rosette (arrow) (HE stain; X20)*

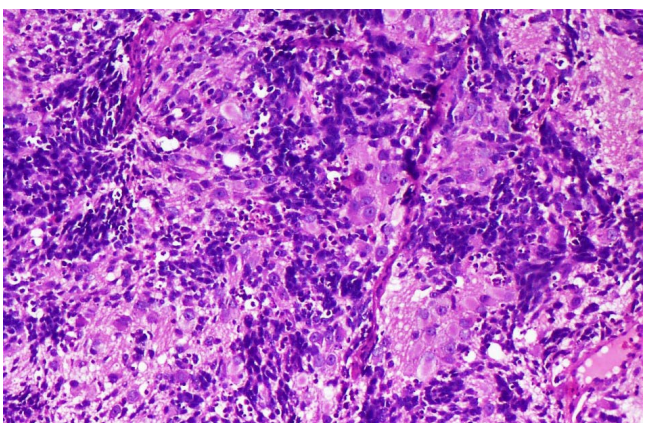

Figure 4: *Foci of ganglioneuroblastic differentiation (HE stain; X200)*

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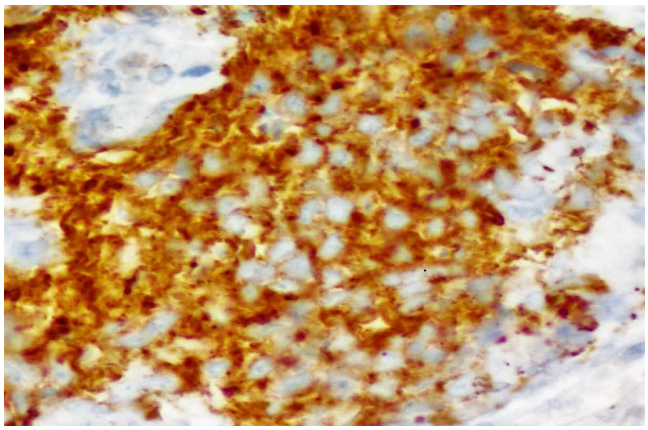

Figure 5: *Synaptophysin positive tumour cells (Immunohistochemistry)*

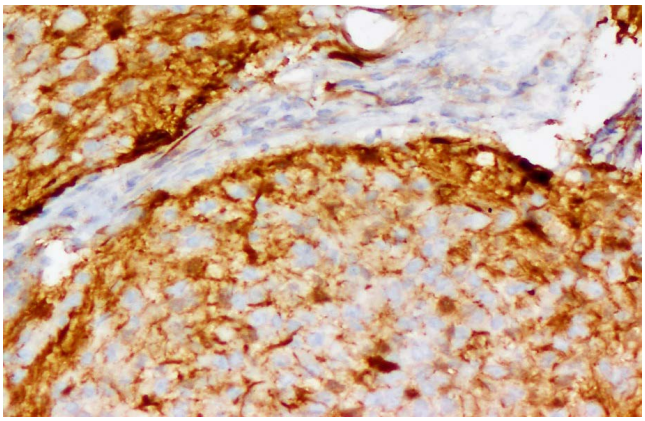

Figure 6: *Sustentacular cells positive for S100 (Immunohistochemistry)*

Three cases had metastases to cervical lymph nodes, two of which were present at the time of diagnosis, and in the other case, it was noted after 5 months of surgical excision of the tumor. One patient was categorized as modified Kadish stage B, four as stage C and three as stage D. The patients with tumors localized to the nasal cavity were treated with surgical excision of the tumor and those with intracranial and intraorbital involvement and/ cervical node metastases were treated with radiotherapy and chemotherapy after resection of the tumor. On follow-up, three patients had recurrence after 4 to 6 months of treatment. (Table 1).

Table1: Case details

S.N.	Age	Sex	Clinical presentation	Radiology-sites involved	Hyams grade	Ganglionic transformation	Treatment	Metastses at the time of diagnosis	Recurrence	Modified kadish stage
1.	73	F	Mass right nasal cavity, nose block, anosmia, pain	Maxillary and sphenoidal sinus, lamina papyracea, Intracranial extension	2	nil	Excision+ CT+ RT	nil	nil	C
2.	30	F	Epistaxis, Blurring of vision	Ethmoid, maxillary sinus, intracranial extension in to frontal & temporal fossa	3	nil	Initial surgical excision, CT+ RT after recurrence of tumor	nil	After 6 months	C
3.	14	F	Epistaxis, Proptosis	Ethmoid & maxillary sinus, orbit, cribriform plate, anterior cranial fossa, cervical lymphnodes	3	nil	Excision +RT+ CT	Cervical nodes	nil	D
4.	60	M	Nose block, Epistaxis	Ethmoid & maxillary sinus	3	Incipient	Initial surgical excision, CT+ RT after recurrence of tumor	nil	Metastases to cervical nodes after 5 months	D
5.	72	M	Nose block, Epistaxis, Anosmia	Nasal cavity, uncinate process, nasal, septum, sphenoid sinus	3	nil	Excision	nil	nil	C
6.	67	F	Nasal block	Ethmoid & Maxillary sinus, cribriform plate, frontal sinus, nasopharynx	2	Focal	Excision + RT	nil	nil	C
7.	42	M	Nasal block, Anosmia, Epistaxis	Ethmoid & Maxillary sinus, nasal cavity	2	Focal	Initial surgical excision. RT given after recurrence of tumor	nil	After 4 months	B
8.	58	F	Nasal block, headache, Epistaxis	Ethmoid & Maxillary sinus, nasal cavity, sphenoid, cribriform plate, cervical lymph nodes	3	nil	Excision, CT+ RT	Cervical nodes	nil	D

M=Male, F=Female, CT=Chemotherapy, RT=Radiotherapy

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DISCUSSION

ENB is a unique malignant tumor of the nasal cavity and paranasal sinuses. The presence of neural filaments in the tumor cells indicates its origin from the neural crest stem cells of olfactory origin. Also, Attwood et al demonstrated intraepithelial neuroendocrine cell hyperplasia in the olfactory groove in their case report of mixed ENB with adenocarcinoma which confirms the cell of origin being neural stem cells of the olfactory neuroepithelium.[6] This tumor is most commonly present in the upper part of the nasal cavity which includes the superior nasal concha, roof of the nose, cribriform plate of the ethmoid, and upper part of the nasal septum.[5] It affects both genders equally, with a bimodal age distribution occurring in ages 11-20 and 51-60 years[1]. Common symptoms include nasal obstruction, epistaxis, pain, anosmia, headache, and proptosis.[1-5] Most of the ENBs are non-functioning tumors. Few of them produce peptide hormones and amines which produce paraneoplastic syndromes which include ectopic ACTH syndrome, syndrome of inappropriate ADH secretion (SIADH), hypertension, hypercalcemia, cerebellar degeneration, and opsoclonus-myoclonus-ataxia.[7] ENB often invades the orbit and skull base. Cervical lymph nodes are the most common sites of metastasis with an occurrence of 10 to 33% at the time of diagnosis. Lung, brain, and bone are the common distant metastatic sites with an occurrence of 12 to 25% at the time of diagnosis.[8]

ENB arises as a polypoidal mass in the roof of the nasal cavity which bleeds excessively on biopsy. On histology, ENB has a distinct lobular architecture composed of sheets and nests of small cells with scant cytoplasm, uniform round to oval hyperchromatic nucleus in a neurofibrillary matrix. Homer-Wright pseudorosettes are seen in lower-grade tumors and Flexner-Wintersteiner rosettes are seen in higher-grade tumors along with foci of necrosis and increased mitoses.[9,10] Hyams grading system which was formulated in the late 80s by the American armed forces institute of Pathology comprises 4 grades- Grade 1 to Grade 4. It is based on the presence or absence of lobular architecture, fibrillary matrix, rosettes, nuclear pleomorphism, mitotic index, and necrosis.[5] (Table 2) ENB is positive for immunohistochemical markers which include synaptophysin, chromogranin, neuron-specific enolase, CD56, neurofilaments, and S100.[7,10] Differential diagnoses which need to be considered and ruled out on histology include neuroendocrine carcinoma, sinonasal undifferentiated carcinoma, rhabdomyosarcoma, melanoma, Ewing sarcoma, and lymphoma.[1,11] (Table 3)

Table 2: Hyam's Grading System

Grade	Lobular Architecture	Fibrillary stroma	Nuclear Pleomorphism	Rosettes	Mitotic activity	Necrosis
I	Present	prominent	Not present	Homer-Wright	zero	absent
II	present	present	mild	Homer-Wright	low	absent
III	May or may not be present	minimal	moderate	Flexner-Wintersteiner	moderate	rare
IV	May or may not be present	absent	marked	None	high	frequent

Table-3: Clinical, histological, and immunohistochemical features of differential diagnosis of ENB

Differential Diagnosis	Incidence in the sinonasal region	Average patient age	Gender predilection	Growth pattern	Characteristic histological features	Neurofibrillary stroma and rosettes	IHC
Sinonasal undifferentiated carcinoma	3-5%	50-60yrs	M>F	nests, wide trabeculae, ribbons, and sheets	Lymphoepitheliomatous morphology	Absent	CK, EMA, P16
Neuroendocrine carcinoma	3%	Small cell type:40-55yrs Large cell type: 49-65yrs	M>F	irregular nests and sheets	Stippled nuclear (salt & pepper) chromatin	Absent	chromogranin, synaptophysin, and CD56 Negative for S100
Rhabdomyosarcoma	<1%	1-10yrs	M=F	Solid sheets and alveolar pattern	Rhabdomyoblasts and cross striations	Absent	Desmin, Myoglobin, Myo-D1, Myogenin
Ewing's sarcoma	2-10%	Children and young adults	M=F	Sheets and lobules	Periodic acid Schiff (PAS) positive cytoplasm	Present	CD99, chromosomal translocation t(11;22) (q24;q12)

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Differential Diagnosis	Incidence in the sinonasal region	Average patient age	Gender predilection	Growth pattern	Characteristic histological features	Neurofibrillary stroma and rosettes	IHC
Melanoma	4%	7th decade	M=F	Sheets and nests	Prominent eosinophilic nucleoli, Melanin pigment	Absent	HMB45, S100, Melan A, SOX10
Lymphoma	3-5%	Children and adults	M>F	Sheets/ nodules	Varies with subtype	Absent	CD45, CD79A, CD20, CD3,
Esthesioneuroblastoma	3-6%	Bimodal: 11-20yrs & 51-60 yrs	M=F	Lobular	Can have divergent epithelial or ganglionic differentiation	Present	Synaptophysin, S100, Neurofilament, Neuron-specific enolase, CD56

ENB with divergent epithelial or ganglionic differentiation and also the occurrence of mixed ENB with adenocarcinoma have been reported in the literature. The diversity of this tumor is possibly due to the pluripotent nature of neural stem cells. Ganglionic differentiation that arises either spontaneously or as a result of chemo and radiotherapy may be local or diffuse.[12-15]

Kadish had proposed a staging system based on the clinical extent of the tumor which was later modified by Morita et al. Modified Kadish staging system includes[16.17]:

Stage A: The tumor is confined to the nasal cavity. **Stage B:** The tumor extends into the paranasal sinuses. **Stage C:** Tumor extends beyond the nasal cavity and paranasal sinuses. **Stage D:** Metastases to cervical lymph nodes or distant sites.

Treatment options include craniofacial surgical resection which can be combined with radiotherapy if margins are positive, for residual lesions and high-stage tumors. Neoadjuvant radiotherapy or chemotherapy is indicated to convert inoperable to operable tumors. Systemic chemotherapy plays a role in the treatment of metastatic tumors.[17-20]

Prognostic factors for ENB are not well established in the literature as the sample size of the case studies conducted to date were small. Low-grade tumors (Hyams grade 1 & 2) have an 80% survival and high-grade tumors (Hyams grade 3 & 4) have a 40% survival.[10] Some authors advocate that age, recurrence, metastasis, and extension to orbit, ethmoid and retropharyngeal area are negative prognostic indicators.[18]

CONCLUSIONS

ENB is an unusual malignant tumor arising from the roof of the nasal cavity and can extend locally into the anterior cranial fossa and the orbit. It has to be differentiated from other small round blue cell tumors by light microscopy and immunohistochemistry. Its potential for divergent epithelial or ganglionic differentiation is noteworthy. It has a marked tendency for recurrence. Hyams grading and Kadish staging are important prognostic factors. A multimodality treatment protocol which includes surgery, radiotherapy, and chemotherapy is necessary.

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