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Successful management of esthesioneuroblastoma with chemoradiotherapy: Report of 3 cases with review of literature

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ABSTRACT

Esthesioneuroblastoma (ENB) is a rare malignant tumour, which arises from the basal progenitor cells of the olfactory epithelium. Histopathological diagnosis is often difficult and is based on antigen detection by immunohistochemistry. The optimal treatment is still debated. Surgery followed by adjuvant radio therapy is the recommended treatment for localised tumour, however, majority of the patients usually present in an advanced stage. We present a case series of three patients who were treated at our Institute with chemotherapy and radiotherapy between the years 2011 and 2016. Although no standard treatment protocol has been established, but combined modality therapy is the cornerstone of treatment for ENB. Chemotherapy can be added in advanced and metastatic disease. None of the patients received definitive surgical treatment. All three patients were treated by radiotherapy and chemotherapy, with endoscopic removal of the tumour done in one case. The patients were disease free during the follow-up period of 48 months, 14 months and 3 months.

Keywords: Esthesioneuroblastoma, Chemoradiotherapy

INTRODUCTION

Malignant neoplasm of nasal cavity is a rare entity. Esthesioneuroblastoma (ENB), also known as olfactory neuroblastoma was first described by Berger and Luc who named it esthésioneuroépithéliome olfactif [1]. It is an uncommon malignant neuroectodermal tumour (NET) of upper nasal cavity and anterior skull base which arises from the basal progenitor cells of the olfactory epithelium. It accounts for less than 3% of all intranasal tumours. Some studies suggest it to have a bimodal age distribution with the peak between 11 and 20 years of age and another peak between the 50th and 60th decade of life [2]. Few others have shown a unimodal age distribution with maximum occurrence at 53 years [3]. The overall incidence is about 0.4 per million population [4]. Patients usually present with unilateral nasal obstruction, epistaxis and headache. Histopathological diagnosis is often difficult as it mimics many other types of intranasal malignancies and is mostly clinched on

immunohistochemistry. Treatment modalities for ENB are surgery combined with radiotherapy (RT) and/or chemotherapy. We report 3 cases of ENB treated at our institute with analysis of the outcome.

CASE SERIES

Patient 1

A 50 year old male presented to our department with complaints of pain on the right side of face, epistaxis and purulent discharge from right side nose since 1 month. He had history of similar complaints 4 months back with a mass in right nasal cavity, for which *functional endoscopic sinus surgery* (FESS) was performed in some private hospital. Endoscopic examination revealed a mass within the right nasal cavity. Histopathological examination (HPE) of the lesion revealed olfactory neuroblastoma/ENB. Contrast Enhanced computed tomography (CECT) demonstrated a residual mass lesion in the superior part of right nasal cavity, which was involving ethmoid sinuses and sphenoid sinus. After reviewing the investigations, patient was staged as Kadish B. He was treated with External Beam Radiotherapy (EBRT) to a dose of 60 Gray in 30 fraction over 6 weeks by cobalt-60 teletherapy after proper consent, following which he was administered 6 cycles of chemotherapy with single agent doxorubicin. A CECT scan, done 2 months after completion of chemotherapy showed tumour in complete remission (CR). Patient was found to be disease free on follow up imaging at 48 months.

Patient 2

A 34 year old male presented to our department with complaints of epistaxis and retro orbital pain since 2 months. On local examination, there was a proliferative mass in the left nasal cavity posteriorly attached to medial surface of superior turbinate. CECT scan showed heterogeneously enhancing mass 2.3x1.2 cm, in the superior part of left nasal cavity, and was localized to it (Kadish stage A). HPE of that mass revealed ENB. Patient was treated with EBRT to a dose of 60 Gy in 30 fractions as patient didn't give consent for surgery. Post radiotherapy local examination and CECT imaging showed residual disease in superior meatus. Patient was discussed in multidisciplinary clinic and as per advice, 6 cycles of chemotherapy with vincristine (O), cisplatin (P), etoposide (E) and cyclophosphamide (C) (OPEC regimen) was administered. A CECT scan done 2 months after the completion of chemotherapy for response evaluation, showed tumour in CR. Patient was lost to follow up after 14 months of completion of the treatment.

Patient 3

An 8 year old male child presented to our department with left eye protrusion and periorbital oedema. He had complaints of epistaxis, lacrimation, and loss of vision in the same side of eye since 3 months. A CECT scan showed 5.2x4.5x6.3 cm well defined lobulated heterogeneously enhancing mass with epicentre in the superior nasal cavity with extension to nasopharynx, sphenoid sinus, cavernous sinus and erosion of body and wing of sphenoid bone, anterior clinoid process and clivus, without any cervical lymphadenopathy. [Fig-1a]

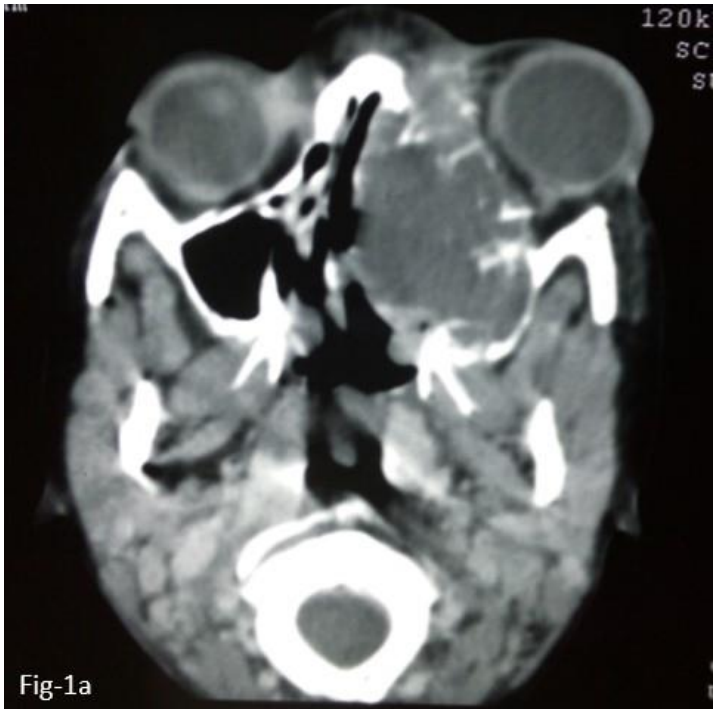


Fig 1a - CECT scan head showing 5.2x4.5x6.3 cm well defined lobulated heterogeneously enhancing mass with superior nasal cavity with extension to nasopharynx, ethmoid sinus, and erosion of body and wing of sphenoid bone.

Histopathological examination of the lesion revealed ENB with immunohistochemical (IHC) confirmation of the findings. [Fig-2a, 2b, 2c]

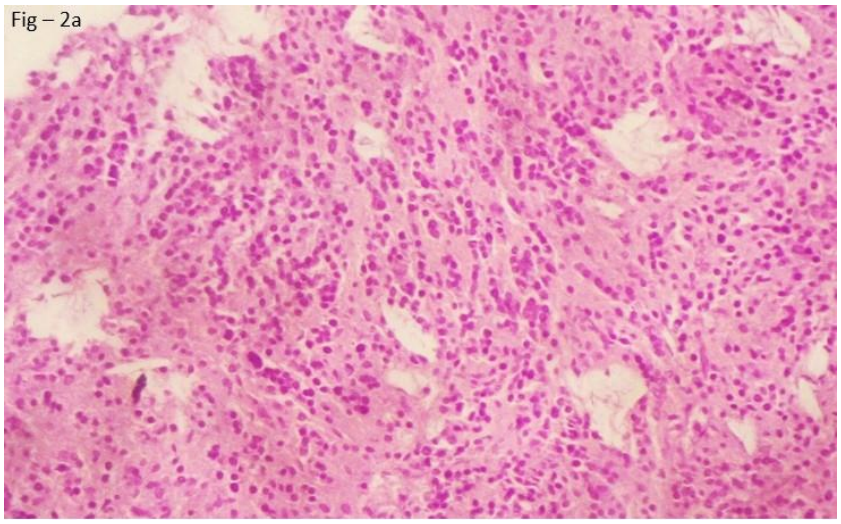
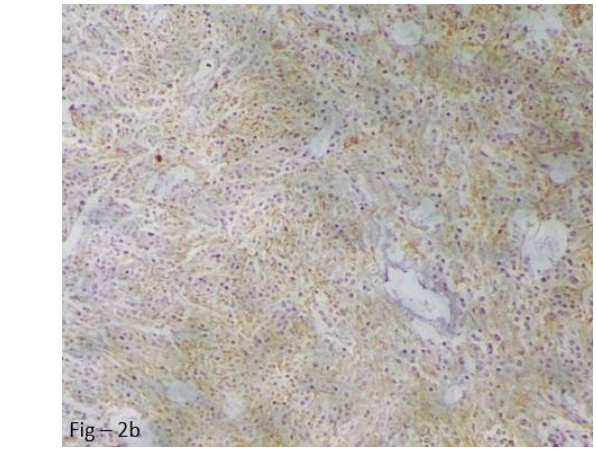


Fig 2a - (20X) Haematoxylin & Eosin section showing sheets and cords of uniform small, blue, round cells with a high nuclear to cytoplasmic ratio. Rosette formation can be seen. The background is fibrillary.



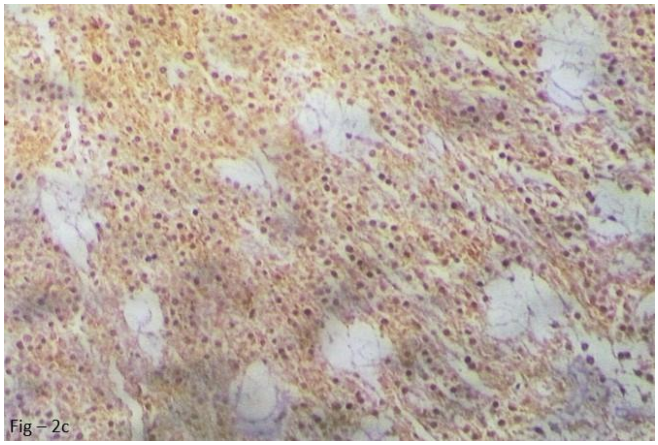


Fig 2b, 2c - (20X) IHC showing positivity for S-100 and synaptophysin respectively.

Patient was discussed in multidisciplinary clinic and was staged as Kadish C. He was administered two cycles of chemotherapy (OPEC regimen) with vincristine (O), cisplatin (P), etoposide (E) and cyclophosphamide (C). Despite the treatment there was no subjective and clinical response and symptoms got aggravated. In view of the poor response to chemotherapy, patient was planned for palliative radiotherapy 30 Gy in 10 fractions. Because of the excellent clinical response, EBRT up to an EQD2 dose of 60 Gy by cobalt 60 teletherapy was administered after proper consent. Post radiotherapy CECT showed well defined hypo dense mass of size 5x3x4.5 cm. [Fig-1b]

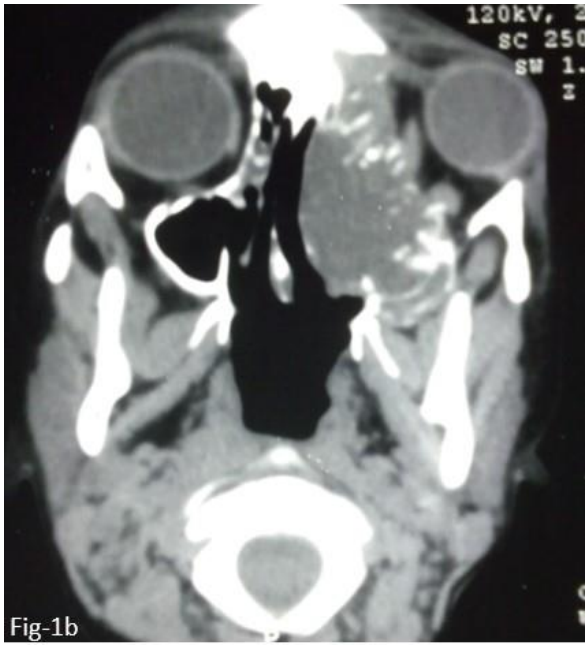


Fig 1b - CECT showing well defined hypodense mass of size 5x3x4.5 cm.

Post radiotherapy, the child received total 12 cycles of chemotherapy with vincristine (V), doxorubicin (A), cyclophosphamide (C) [6 cycles of VAC] alternating with ifosfamide (I) and etoposide (E) [6 cycles of IE]. After one month of completion of chemotherapy, repeat CECT showed no significant enhancement in well-defined lobulated mass in nasal cavity which measured 3.2x1.8 cm, suggestive of a good response. [Fig-1c]

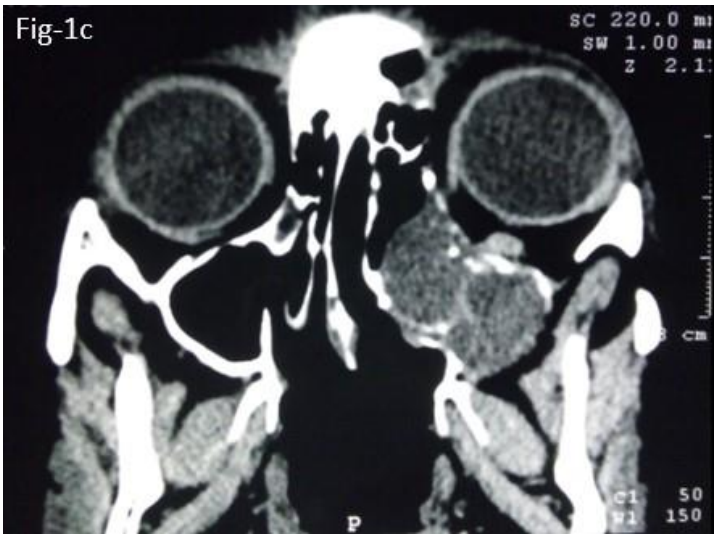


Fig 1c - CECT showing no significant enhancement in well-defined lobulated mass in nasal cavity measuring 3.2x1.8 cm.

Thereafter the patient was kept on regular follow-up with serial imaging which showed no evidence of active disease.

DISCUSSION

Esthesioneuroblastoma, an uncommon malignant neoplasm of olfactory tract, is synonymous with olfactory esthesioneuroma, neuroesthesioma, olfactory neurocytoma and olfactory neuroblastoma. ENB is a rare locally aggressive tumour. Although it can be found in all age groups, it seems to occur more commonly in the second and fifth decades of life with equal gender predilection. The three patients reported in our study belong to different age groups. The most common symptoms are unilateral nasal obstruction; frontal headache and diplopia are seen in locally advanced disease when the disease involves the adjacent structures. Because of these nonspecific symptoms, 70% of patients present with advanced-stage disease [5,6]. ENB is a rare neoplasm of neuroectodermal origin that arises from olfactory epithelium in the upper nasal cavity at the level of the cribriform plate. The pathogenesis is not well understood, however, viral infection (specifically polyoma virus) has been proposed to be a causative factor by Lin et al. [7]

There is no consensus on the best staging system for ENB. Kadish system is the first (described in 1976) and most popular staging system. [8] [Table -1]

Table 1 – Kadish staging system for esthesioneu roblastoma

Stage A	Disease confined to nasal cavity
Stage B	Disease confined to nasal cavity and one or more paranasal sinuses
Stage C	Disease extending beyond nasal cavity or para nasal sinuses; including involvement of orbit, base of skull, or intra cranial cavity, cervical lymph nodes, or distant metastasis

Morita et al modified the Kadish system by establishing stage D for tumour with metastasis. [9] CECT imaging is essential for correct staging and should be evaluated carefully for erosion of bones. An unusual but characteristic imaging feature of ENBs is the presence of cysts at the tumour-brain interface.[10] Magnetic Resonance Imaging (MRI) is often necessary to better delineate sinonasal, intraorbital extension or an intracerebral extension. Since most ENBs express somatostatin receptors, use of scintigraphy with a radiolabeled somatostatin analog (Octreoscan) has been proposed [11]. Histopathological diagnosis is often difficult in most of the cases and is based on antigen detection by immunohistochemistry.

Owing to the low incidence, there are no standard guidelines recommended for the optimal treatment of ENB. The natural history of disease, which ranges from slow progression to aggressive local spread and sometimes distant metastasis, has yielded various treatment protocols and recommendations starting from single modality therapy to multidisciplinary approach with surgery, radiotherapy and chemotherapy in various combinations [12] Standard treatment protocols have dramatically improved the overall survival rate in patients with ENB since Berger et al first described the disease. Earlier the standard treatment was external craniofacial resection followed by postoperative radiotherapy for low to moderate grade lesions (Kadish stage A and B) with addition of chemotherapy for recurrent or advanced and metastatic disease (Kadish stage C). However, local recurrence rates are still on higher side and are reported to be 58 – 62% [2, 3, 13]. Off late, endoscopic surgery for olfactory neuroblastoma followed by adjuvant treatment has been shown to have good survival rates with less morbidity [2].

Dulguerov et al reported a 5 year survival rate of 45% [13]. Others have reported it to be as high as 70%. Prognosis depends upon stage and grade of the tumour. Surgery and postoperative radiotherapy have been shown to be significant predictors of disease specific survival in high grade tumours [14]. Age more than 50 years, female gender, tumour recurrence and metastasis are considered as negative prognostic factors [15].

To our knowledge, less than 1000 cases of ENB have been reported in literature [15]. We present 3 such cases [Table 2] treated at our hospital including one paediatric ENB. All the three cases were treated with chemo-radiotherapy.

Table 2 – Cases of esthesioneuroblastoma

	Patient 1	**Patient 2**	**Patient 3**
Age, Sex	50 years, male	34 years, male	8 years, male
Diagnosed on	November 2011	February 2012	January 2015
Stage at presentation (Kadish stage)	Stage B	Stage A	Stage C
Treatment modality given	Surgery f/b radiotherapy f/b chemotherapy	Radiotherapy f/b chemotherapy	Chemotherapy f/b radiotherapy f/b chemotherapy
Surgery	FESS	NIL	NIL
Radiotherapy dose	60 Gy in 30 fractions	60 Gy in 30 fractions	60 Gy in 30 fractions
Chemotherapeutic agents and number of cycles	Single agent doxorubicin – 6 cycles	OPEC – 6 cycles	OPEC – 2 cycles VAC – 6 cycles IE – 6 cycles
Response of tumour	CR during follow up	CR during follow up	Significant response – no enhancing mass lesion
Last review	March 2014	January 2013	On follow up – last review on April 2016

OPEC – Vincristine (O), Cisplatin (P), Etoposide (E) and Cyclophosphamide (C)
VAC – Vincristine (V), Doxorubicin (A) and Cyclophosphamide (C)
IE – Ifosfamide (I) and Etoposide (E)
FESS – *Functional endoscopic sinus surgery*
CR – Complete remission

One of them presented with locally advanced disease (Kadish stage C), which was inoperable and initially did not respond to chemotherapy (OPEC regimen) but showed significant response to radiotherapy and a different regimen of chemotherapy. Although no standard treatment protocol has been established, we strongly recommend surgery followed by radiotherapy is an excellent paradigm for these tumours in early stage and chemotherapy should be considered in advanced and metastatic setting.

CONCLUSION

ENB is a rare malignant tumour of neural crest origin arising from olfactory epithelium, which may present as local, loco-regionally advanced to widely metastatic disease. The etiology and pathogenesis is poorly understood. The combined use of CECT and MRI techniques is an excellent informative tool for treatment planning. Kadish system is useful in staging of the disease and for deciding therapeutic approach. Surgical resection followed by adjuvant radiotherapy with dose of 50 -60 Gy is the most usual treatment and some modification can be done according to the disease and patient profile.

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