IMPROVED OUTCOME WITH MULTIMODAL MANAGEMENT OF ADVANCED ESTHESIONEUROBLASTOMA

(Report of Two Cases)

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Introduction

Esthesioneuroblastoma is an uncommon neuro-epithelial tumour of nasal cavity and paranasal sinuses, representing 1-5 per cent of the tumours arising from nasal cavity [1,2]. In literature, about 300 cases have been reported so far [2]. It occurs in a wide age range of patients, 3 years to 90 years, with a peak at second and third decade and a second peak at sixth and seventh decades of life [1]. Majority of patients present with epistaxis, nasal obstruction, rhinorrhoea, while others may present with lacrimation, diplopia, proptosis, anosmia. Rare presentations include hormone excess syndromes, such as inappropriate antidiuretic hormone secretion [3], ocular mass [4] and isolated fourth cranial nerve palsy [1]. Regional lymph node involvement and distant metastasis are rare. The diagnosis is suspected on clinical grounds and confirmed by, histo-pathological examination of representative biopsy and histo-chemical, and occasionally immunological studies [1,2]. Standard treatment has been surgery or radiotherapy or both. Chemotherapy has been used in limited patients in the past and encouraging results are reported now. Prognosis of the treated cases has improved and 5 year overall survival ranges from 40-90 per cent [1,2].

At our centre, 4 cases have been registered over last 15 years. Two cases treated in the past with radiotherapy alone were lost to follow up. Presently reported 2 patients with stage C disease were managed by concurrent chemotherapy and radiotherapy resulting in complete clinical and pathological responses. These cases are presented in view of rarity of the condition and excellent response to multi-modal therapy.

Case No 1

A 23-year-old male patient presented with epistaxis and examination revealed a polyp in the left nasal cavity. With a diagnosis of nasal polyp he was subjected to polypectomy. He remained asymptomatic and 6 months later had rhinorrhoea, blood stained discharge and nasal obstruction. General and systemic examination were within normal limits. ENT examination revealed a polypoidal, pink fleshy mass in the left nasal cavity with blood stained discharge. There was no proptosis, or evidence of CNS involvement. Left tympanic membrane was blue and there was conductive deafness. Haemogram, urine examination, biochemical parameters, radiograph of chest and angiogram were normal. Radiograph of paranasal sinus (PNS) revealed hazy left maxillary sinus. With a diagnosis of recurrent polyp, he was subjected to polypectomy again but complete resection was not possible. He was transferred to our centre and was further evaluated. Clinically, there was a friable growth in the left nasal cavity, which bled on touch. There was no lymphadenopathy and systemic examination was non-contributory. CT scan (Fig 1) of the paranasal sinuses revealed - soft tissue mass in left ethmoid sinus, with expansion of lateral wall, absent medial wall of left maxillary sinus, thickened sphenoid sinus wall and attenuation of left orbital floor. In the right maxillary sinus, there was a soft tissue mass which disappeared after a course of antibiotics and hence was considered to be of infective origin.

Fig. 1 : CT Scan of paranasal sinuses (Case no 1), (Pretreatment)

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Fig. 2 : Photomicrograph of the biopsy (Low power)

Histological examination revealed sheets of medium sized round cells with high nuclear cytoplasmic ratio, and frequent mitosis and haemorrhage (Fig 2). Immunohistochemistry revealed positivity for neurone specific enolase and negativity for leucocyte common antigen. A diagnosis of esthesioneuroblastoma stage C [5] was made. As the tumour was not considered resectable, he was taken up for concurrent chemotherapy and radiotherapy. Combination chemotherapy consisted of cyclophosphamide (990 mg/m^2), vincristine (1.4 mg/m^2), doxorubicin (40 mg/m^2), cisplatin (75 mg/m^2). A total of 6 cycles were administered at 3 weekly intervals over 6 months. External radiotherapy of 5580 cGy was delivered in 31 fractions, over 49 days, concurrently with chemotherapy. The therapy related complications encountered were febrile neutropenia and oral mucositis from which the patient recovered uneventfully. On completion of planned therapy, there was no clinical evidence of disease. However, CT scan of the PNS showed the presence of residual opacity in the left maxillary sinus (Fig 1B). With an aim of resecting the residual mass, he was taken up for partial maxillectomy (maxillectomy without disturbance of orbital roof and its contents and ethmoidectomy) followed by an internal obturator fitting. Postoperative period was uneventful. Histo-pathological examination of the resected tissue did not reveal any evidence of malignancy. Thereafter, the patient has been on a regular follow-up and remains disease free 3 years after diagnosis with near normal facial appearance.

Case No 2

A 29-year-old male patient presented with recurrent epistaxis from left nostril and left orbital prominence. On examination, there were hypertrophied inferior turbinates and no other abnormality was detected. He was managed as a case of sinusitis, with little improvement and 4 months later had increasing proptosis of left eye, nasal obstruction, epistaxis and foul smelling purulent discharge from left nostril hence referred to our centre. There was a friable mass in the left nasal cavity extending upto the nasopharynx on anterior and posterior rhinoscopy, with a blood stained purulent discharge. Maxillary tenderness, was present and the left tympanic membrane was retracted and lustreless. Left eye had proptosis (Exophthalmometry- 102 mm RT 18 mm LT 26 mm) with increased orbital temperature and restriction of ocular movements. There was fundal hyperaemia and the vision was well preserved. He was in a good performance status and systemic examination was normal. Haemogram, urinalysis, biochemical parameters and radiograph of the chest were normal. CT scan of PNS and brain revealed a large naso-ethmoidal mass with patchy destruction of medial walls of the orbits and maxillary sinus. The soft

Fig. 3 : Post treatment CT Scan of paranasal sinuses (Case no 2)

tissue mass had filled up the entire maxillary sinus and extended into the orbit. The orbital muscles were not well visualised and the left sided turbinates were destroyed completely. There was no intra-cranial extension. Biopsy of the mass revealed similar histological features as case No 1. The final diagnosis was that of esthesioneuroblastoma stage C [5]. As the resection was not considered possible, he was taken up for concurrent chemo-radiotherapy. Combination chemotherapy regime was similar to the regime used in first patient. Concurrent radiotherapy in dose of 5400 cGy in 30 fractions over 68 days was delivered. Patient experienced side effects of neutropenia and oral mucositis with uneventful recovery. Assessment with CT scan, after 4 cycles of combination chemotherapy and radiotherapy indicated that there was a residual tumour in the maxilla. With an impression of partial response (PR), he was managed with an alternate regime of combination chemotherapy consisting of ifosfamide, (1.3 G/m^2), etoposide (100 mg/m^2), doxorubicin and cisplatin (in same doses). On assessment at the end of 6 cycles of alternate chemotherapy, there was no evidence of disease on clinical examination. CT scan of the PNS (Fig 3) had revealed a soft tissue lesion in the left maxillary sinus, which on biopsy did not exhibit any evidence of malignancy hence further surgery was not contemplated. Presently he is asymptomatic and has completed 3 years recurrence free follow up.

Discussion

Esthesioneuroblastoma, also known as 'olfactory neuroblastoma' is rare neural tumour of the nasal cavity and is the most malignant of the olfactory neurogenic tumours. The histogenesis of the tumour is not yet completely clear. The tumour arises from the basal cells of olfactory epithelium situated in the cribriform plate, superior nasal septum, and the superior nasal turbinates. After histological diagnosis, a complete staging evaluation is necessary to determine the extent of the tumour, with CT scan of the paranasal sinuses, brain, radiograph of chest and where possible MRI scans. Presently followed staging system (Kadish et al 1974) consists of stages A, B and C. In stage A the tumour is limited to nasal cavity, while in stage B tumour extends beyond cavity but is confined to one or more paranasal sinuses. In stage C tumour extends beyond the nasal cavity and paranasal sinuses and may

extend to the orbit, base of skull, or intracervical lymph node or there may be distant metastasis [5].

Till recently surgery and radiotherapy have been employed for treatment of this condition, while the experience with chemotherapy has been limited. Standard therapy has been craniofacial resection followed by postoperative radiotherapy. Various surgical procedures (usually via a lateral rhinotomy approach) employed are excision, ethmoidectomy, medial maxillectomy, with or without frontal or sphenoid sinusotomy determined by extent of tumour [6]. Radiotherapy used as postoperative adjuvant or palliative therapy for unresectable tumours, consists of external beam in the doses of 45 to 60 Gy using multi-field technique, depending on the extent of the tumour. With surgery and radiotherapy encouraging results have been reported in early cases but on long-term follow up, 57 to 75 per cent patients have local recurrences [6]. Mostly recurrences occur within 2 years, but can be as early as 7 months and as late as 10 years. Extension to brain occurs in 48 per cent patients. Five year overall survival rate has been 58 per cent and disease free survival 20 per cent [7].

The chemo-responsiveness of esthesioneuroblastoma has recently been documented [1,2,5,7-9]. With 1 or 2 drug regimen limited responses of short duration were noted but with maturing experience, better results have been observed. Spaulding et al demonstrated that the recurrences were delayed with use of chemotherapy and radiotherapy followed by cranio-facial resection [7,8]. Schwaab et al used a combination of vincristine and cyclophosphamide in 6 patients and demonstrated 62 per cent response rates [7,8]. Wade et al reported his experience with 2 drugs in 8 patients, and observed 2 complete responses, 4 partial responses and 2 no responses with a median duration of response being 1 year and 2 months [7,8]. With the advent of combination chemotherapy the responses have been long lasting and there has been a longer disease free survival and overall survival. Recently, the use of high dose chemotherapy followed by autologous bone marrow transplantation (ABMT) [9], has demonstrated increased duration of responses with survival benefit in a small study of 5 patients. To evaluate the role of chemotherapy, a randomized trial has not been possible due to rarity of the disease. However, it is certain that the addition of chemother-

apy can improve the results in patients of esthesioneuroblastoma, especially in delaying recurrences, as well as prolonging the recurrence free and overall survival [1,2,9]. On completion of therapy, the patients should be on a lifelong follow-up as the late recurrences can occur [1,2].

Both of our patients had stage C disease on presentation and have been managed with concurrent chemotherapy and radiotherapy, resulting in complete clinical and pathological responses. One has undergone resection of the residual mass. Both have completed 3 years of disease free survival. Our observation of complete response further reiterates that the addition of aggressive chemotherapy to multimodal therapy can improve the local responses and survival in advanced cases. As a large conclusive trial cannot be expected due to the rarity of the tumour, it may be reasonable to infer from these small experiences, that inclusion of a multi-drug combination chemotherapy is essential in management of advanced esthesioneuroblastoma.

REFERENCES

1. O'Connor Timothy A, McLean Patrick, Julliard JF, Parker Robert G. Olfactory Neuroblastoma. *Cancer* 1989; 63: 2426.
2. Obsen Kerry D, DeSante Lawrence W. Esthesioneuroblastoma - Biological and clinical behaviour. *Arch Otolaryngol* 1983; 109: 797-802.
3. Al Ahwal M, Jha N, Nabholtz JM, Hugh J, Birchall I, Nguyen GK. Olfactory Neuroblastoma: report of a case associated with inappropriate anti-diuretic hormone secretion. *J Otolaryngol* 1994; 23(6): 437-9.
4. Bobele GB, Sexauer C, Barnes PA, Krous HF, Bodensteiner JB. Esthesioneuroblastoma presenting as an orbital mass in a young child. *Med Paediatr Oncol* 1994; 22(4): 269-73.
5. Kadish S, Goodman M, Wang CC. Olfactory Neuroblastoma. *Cancer* 1974; 37: 1571-6.
6. Levine PA, Debo RF, Merdith SD, Jame JA, Constable WC, Cantrell RW. Cranio-facial resection at University of Virginia (1976-1992): Survival analysis. *Head Neck* 1994; 16: 574-7.
7. Walters R Thomas, Pushparaj N, Ghander Atif Z. Olfactory Neuroblastoma - Response to combination chemotherapy. *Arch Otolaryngol* 1980; 106: 242-3.
8. Wade PM Jr, Roy E Smith, Johns ME. Response of Esthesioneuroblastoma to Chemotherapy. *Cancer* 1984; 53: 1036-41.
9. Eden BV, Debo RF, Larner JM, Kelley MD, Levine PA, Stewart FM, Cantrell RW, Constable WC. Esthesioneuroblastoma: Long-term outcome and pattern of failures- the University of Virginia experience. *Cancer* 1994; 73: (10) 2556-62.