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Esthesioneuroblastoma

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Abstract

Introduction: To review all cases of esthesioneuroblastoma in Qaem Hospital from 1990 to 2004 with respect to Clinical findings image studies, staging, grading, histopathological and prognostication.

Materials and Methods: Possible cases of esthesioneuroblastoma were retrieved from Neurosurgery, Otorhinolaryngology And Pathology departments. Patients were included on the basis of review of their files or pathology reports. Thirteen possible cases were retrieved. One case was excluded because of no documented pathology. Esthesioneuroblastoma is a malignant neuroendocrine tumor originating in the olfactory mucosa. It is a small blue cell neoplasm with a characteristic lobular architecture. The tumours were staged according to Kadish staging system and Kaplan-Meier survival analysis was used to identify prognostic factors.

Conclusions: The Kadish staging system was able to group the patients into prognostically relevant groups. Intracranial involvement and metastases at the time of diagnosis were found to be poor prognostic factors.

Keywords: Esthesioneuroblastoma, Histopathology, Survival analysis, Immunohistopathology.

Introduction

Esthesioneuroblastoma is an uncommon malignancy of olfactory neuroepithelium. It is a small blue cell neoplasm with a characteristic lobular architecture. It has a neuroendocrine immunophenotype that was first recognized in 1924 by Berger et al. (1,2,3) The anatomic origin in the superior nasal cavity often leads to non-specific symptoms that preclude early diagnosis.

As a result, most patients present with locally advanced disease that involves the paranasal sinuses or anterior cranial fossa through the cribriform plate.

Optimum management for esthesioneuroblas-toma is poorly defined because of the rarity of the disease and changes in imaging, surgery and radiotherapy (RT).

The purpose of this study is to review our experience with esthesioneuroblastoma, with respect to Clinical findings image studies, staging, grading, histopathological and prognostication.

Materials and Methods

Possible cases of esthesioneuroblastoma in the period 1990–2004 were retrieved from the files of the Neurosurgery and ENT Departments, clinical records from all patients were scrutinized and clinical data and roentgen graphic findings were recorded. The patients were staged according to Kadish (Table1). Intracranial involvement at the time of diagnosis was recorded, as was the presence of metastasis. Available paraffin-embedded tissue and/or glass slides were collected and reviewed by pathologists.

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The tumours were graded according to Hyams. In cases where no tissue or only old glass slides were available, the primary pathology reports were analyzed and based on these patients were included or excluded.

Results

A total of 13 cases of possible esthesione -uroblastoma were retrieved. One case was unavailable for review. 12 cases were available for histopathological review.

Thus, a total of 12 patients were included in the present study. These patients had a median age of 41 (range 9–72) years. One patient was Kadish stage A (9.7%), 4 were stage B (33.5%), and 7 were stage C (58.3%). Five of the patients with stage C had intracranial involvement and one patient had metastases to cervical lymph nodes at the time of diagnosis. We found a 61% 5-year crude survival rate with a median crude survival of 3.1 years (range 0.3–19.2 years).

Relapse-free survival was 50% with a median value of 1.7 years (range 0–19.2 years). Demographics and Initial Signs or Symptoms of Patients are summarized in (Table 2), and Treatment and Outcome in (Table 3).

Table 1: Kadish staging system

Stage	Tumor extension
A	Tumor limited to nasal cavity
B	Tumor limited to nasal cavity
C	Tumor extending beyond the nasal cavity and paranasal sinuses

Table 2: Demographics and Initial Signs or Symptoms in 12 Patients With Esthesioneuroblastoma

Patient No.	Age (y)	Gender	Stage	Presentation
1	9	F	B	Anosmia, nasal obstruction
2	13	F	C	Epistaxis, nasal obstruction
3	48	F	B	Nasal obstruction
4	47	F	C	Nasal obstruction
5	36	M	C	Facial pain
6	46	M	C	Nasal obstruction, anosmia
7	19	M	C	Proptosis, epistaxis, visual changes Cranial nerve III paresis
8	67	M	C	Nasal obstruction, anosmia, epistaxis
9	72	M	C	Diplopia, anosmia, headaches, proptosis Epistaxis, epiphora, nasal obstruction
10	57	M	B	Epistaxis, Proptosis
11	59	F	C	Nasal obstruction, epistaxis, anosmia
12	61	M	B	Epistaxis, anosmia, Proptosis

Table 3: Treatment and Outcome of 12 Patients With Esthesioneuroblastoma

Patient No	Initial Treatment.	Recurrence	Time to Recurrence(mo)	Salvage Therapy	Final Status	Time of Follow-Up (mo)
1	CFR	Local	8	NCFR+ RT	NED	162
2	NCFR	None			Dead without disease	60
3	NCFR	Local	121	CRR + RT	NED	175
4	CFR + RT	Local	51	NCFR	Dead of disease	89
5	CT+ CFR + RT	Regional	5	RND+ RT	Dead of disease	31
6	CFR + RT	None			NED	22
7	Definitive RT	None			Dead without disease	6
8	Pre operative RT + Surgery*	Unknown			Lost to follow-up	36
9	Debulking Palliative RT	Persistent			Dead of disease	15
10	CFR	None			NED	10
11	NCFR + RT	Local	140	Surgery*	NED	212

***Surgery of nonspecified technique. NED: no evidence of disease CFR: craniofacial resection**
NCFR: non-craniofacial resection; RT: radiotherapy CT: chemotherapy RND: radical neck dissection

Discussion

Esthesioneuroblastoma is a rare malignancy of the neuroepithelium. Fewer than 1,000 cases have been reported in the literature; and most of the reports were in small series similar to the present study. Pathological classification is challenging because these tumors must be differentiated from other small blue cell neoplasm of the nasal cavity such as lymphoma, sarcoma, and melanoma (2,4,6).

Differentiating esthesioneuroblastoma from neuroendocrine carcinoma is difficult and some think the entities are a continuous spectrum with varying biological aggressiveness. In 1979 Elkon reviewed the existing literatureand reported a bimodal age distribution with an early peak from 11 to 20 and a later peak between 51 and 60 years of age (2).

The current study reports a median age at diagnosis of 41 years, which is consistent with the later peak. The Kadish staging system for esthesioneuroblastoma has been widely used in the literature.The inadequacies of this system have been pointed out by Dulguerov et al (12).First, few patients have group A disease if the staging is strictly applied because of a high incidence of ethmoid sinus involvement. There was only one patient in our experience who presented with stage A disease.

Similar observations have been reported in other series, and the overall incidence of Kadish A disease is estimated at 5% (5,10,14,15).

Modern imaging makes a diagnosis of Kadish A disease less likely. A second weakness is the lack of a clear prognostic significance of stage A and B disease. This may be because sinus involvement does not adversely impact surgical resectability and hence should not represent an adverse prognostic factor.

A third weakness is that most tumors are stage C disease, which includes tumors with a spectrum of spread patterns and biological behaviors that should have prognostic significance. Finally, the regional disease was not included in the staging system because of its rarity.

Some have suggested this should be classified as Kadish D disease (5). Despite the inadequacies and attempts to use a TNM classification, Kadish staging is the most commonly used and hence applied to our patients (3,12).

Optimum management for esthesioneuroblastoma remains to be defined. It is difficult to achieve en bloc resection with adequate margins using extracranial surgery alone (3,4,16).

Therefore, CFR coordinated with neurosurgery, otolaryngology, and ophthalmology has become the most commonly used surgical procedure for esthesioneuroblastoma

Despite aggressive CFR, local recurrences after surgery alone occur in 20% to 60% of cases depending on the length of follow-up.

Adjuvant RT is recommended for advanced (stage B or C) disease even after a complete resection to improve local control (5,6,12).

The potential benefit of preoperative RT with or without chemotherapy has also been reported (10).

Foote et al. reported improved local control (87% vs. 41%) after postoperative radiation compared with surgery alone despite a selection bias against combined modality therapy (7).

Patients treated with surgery and RT had a higher proportion of advanced disease (81% vs. 41% stage C) and high grade tumors (38% vs. 14%) in comparison to the surgery alone group. Ahmad et al. reported the University of Michigan experience and found no local failure in six patients who received 6000 cGy or more of postoperative RT despite incomplete resection in 4 of the 6 patients (17).

Despite combined modality therapy and advances in surgical techniques and RT technology, frequent locoregional recurrence remains a significant problem.

Eden et al in a review of 40 patients, noted a recurrence rate of 55% after combined modality therapy (18). Two thirds of the recurrences were locoregional and 39% occurred after 5 years of follow-up.

The Mayo Clinic experience reported a similar 5-year local recurrence rate of 35% (5,20). The present series confirmed these findings with the 5- and 10-year actuarial disease-free survival rate of only 56% and 42%, respectively.

Elective treatment of the neck is controversial. Kadish, (11) reported that less than 15% of patients developed cervical lymph node metastasis; therefore, elective treatment was unnecessary. In contrast, a much higher rate of neck disease(20%–44%) has been reported in patients with locally advanced disease (19–21).

The present series noted two regional recurrences that occurred in the setting of advanced disease or after local recurrence. The experience with chemotherapy (CT) for esthesioneuroblastoma is lacking and underreported. Traditionally, CT has been reserved for unresectable, recurrent, or metastatic disease.

Preoperative CT with RT has gained attention in recent years (4,7–10,14). Polin et al. updated the University of Virginia experience and concluded preoperative CT with RT to be advantageous for all patients with esthesioneuroblastoma (10). We did not observe any significant response after induction chemotherapy in two patients. Esthesioneuroblastoma commonly recur after 5 or more years of follow-up.

The Mayo Clinic series noted 42% of local recurrences developed beyond 5 years of initial treatment with the longest duration to first recurrence at 10 years after initial treatment (20). Eden et al.18 reported 39% of recurrences beyond 5 years. Our experience found four local recurrences after a mean interval of 7.2 years, and two of those events were observed more than 10 years after initial treatment.

The importance of aggressive salvage therapy for recurrent esthesioneuroblastoma has been recognized. Morita et al (20).

Noted a 43% salvage rate and a 5-year survival rate of 82% after salvage therapy. We observed that 3 of 4 local recurrences were successfully salvaged with either surgery alone or in combination with additional postoperative RT.

These patients remain alive with no evidence of disease 3, 9, and 12 years after their first salvage procedures although two have required additional salvage therapy. The fourth underwent additional surgery and was disease-free for 2 years until the development of a second local recurrence.

Treatment complications in patients with esthesioneuroblastoma remain high. This is, at least in part, reflective of aggressiveness and difficulty in management of this disease. As demonstrated in this study, visual impairment is the most common adverse effect of the treatment. Because of the location of esthesioneuroblastoma, it is difficult to deliver an adequate dose of radiation without exceeding the tolerance dose of the critical structures such as the brain, optic chiasm, optic nerves, and orbits (22,23).

Dulguerov et al. 12 reported a 29% incidence of complications, and 24% were related to radiotherapy. All resulted in a poor-to-nonfunctional eye after conventional radiotherapy. Ahmad et al (17).

Observed one incidence of hematoma in optic chiasm 29 months after postoperative RT. This patient received 6706 cGy in 34 fractions to the optic chiasmal region. Improved radiotherapy, such as intensity modulated radiotherapy and proton beam, may allow a higher and more accurate tumoricidal dose to be delivered without an increased risk of complications.

Conclusion

Our series, although limited by small numbers of patients, confirms previous observations and highlights the long natural history of esthesioneuroblastoma. Despite combined modality therapy, local and regional recurrences occur frequently.
Salvage therapy is often effective and long-term survival afterward is common.

More effective local control using improved imaging, surgery, and radiotherapy may be possible. The Kadish staging system was able to group the patients into prognostically relevant groups. Intracranial involvement and metastases at the time of diagnosis were found to be poor prognostic factors.

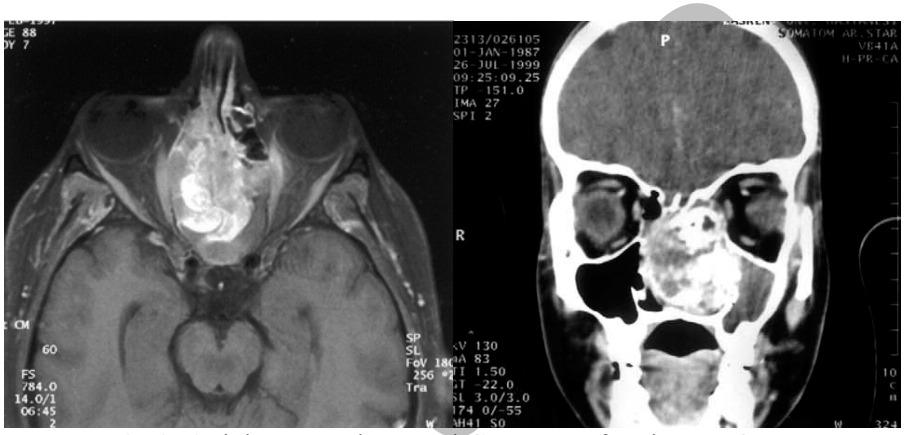

Fig.1: Axial MRI and coronal CT scans of patient No2

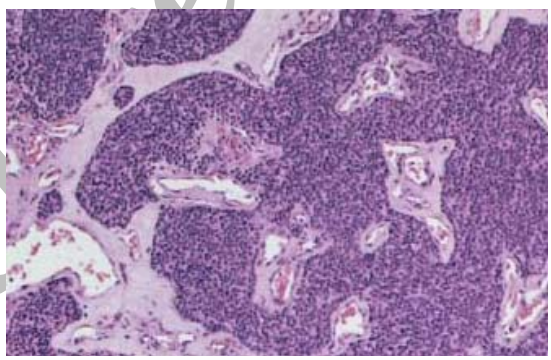

Fig. 2: Lobular esthesioneuroblastoma with a vascular-rich stroma.

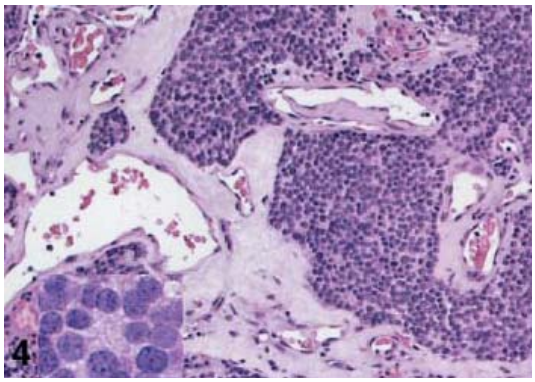

Fig. 3: Lobular esthesioneuroblastoma with a pseudorosette

References

1- Ingeholm P, Sune A. Esthesioneuroblastoma: A Danish Clinicopathological study of 40 consecuative cases. APMIS 2002; 110:639-645

2- James HS, Weining Z. Esthesioneuroblastoma. Laryngoscope 2001;111: 488-494

3- Berger L, Luc R. Esthe´sione´ uroe ´pithe liome olfactif. Bulletin deL' Association Francaise pour l'Etude du Cancer 1924; 3: 410–421.

4- Elkon D, Hightower SI, Lim ML, Cantrell RW, Constable WC. Esthesioneuroblastoma. Cancer 1979; 44: 1087–1094.

5- Biller HF, Lawson W, Sachdev VP, Som P. Esthesioneuroblastoma: surgical treatment without radiation. Laryngoscope 1990;100: 1199–1201.

6- Levine PA, McLean WC, Cantrell RW. Esthesioneuroblastoma: the University of Virginia experience 1960–1985. Laryngoscope 1986;96: 742–746.

7- Foote RL, Morite A, Ebersold MJ et al. Esthesioneuroblastoma: the role of adjuvant radiation therapy. Int J Radiat Oncol Biol Phys 1993;27: 835–842.

8- Walters TR, Pushparaj N, Ghander AZ. Olfactory neuroblastoma: response to combination chemotherapy. Arch Otolaryngol 1980;106: 242–243.

9- Koka VN, Julieron M, Bourhis J, et al. Aesthesioneuroblastoma. J Laryngol Otol 1998;112:628–633.

10. Polin RS, Sheehan JP, Chenelle AG, et al. The role of preoperative adjuvant treatment in the management of esthesioneuroblastoma: the University of Virginia experience. Neurosurgery 1998; 42: 1029–1037.

11- Kadish S, Goodman M, Wang CC. Olfactory neuroblastoma: a clinical analysis of 17 cases. Cancer 1976; 37: 1571–1576.

12- Dulguerov P, Calcaterra T. Esthesioneuroblastoma. The UCLA Experience 1970–1990. Laryngoscope 1992; 102: 843–849.

13- Kaplan EL, Meier P. Nonparametric estimation from incomplete observation. Journal of the American Statistical Association 1958; 53:457–481.

14- Jekunen AP, Kairemo KJA, Lehtonen HP, Kajanti MJ. Treatment of olfactory neuroblastoma; a report of 11 cases. Am J Clin Oncol 1996;19:375–378.

15- Slevin NJ, Irwin CJR, Banerjee SS, Gupta NK, Farrington WT. Olfactory neural tumors the role of external beam radiotherapy. J Laryngol Otol 1996; 110: 1012–1016.

16- Newbill ET, Johns ME, Cantrell RW. Esthesioneuroblastoma: diagnosis and management.South Med J 1985;78:275–282.

17- Ahmad K, Fayos JV. Role of radiation therapy in the treatment of olfactory neuroblastoma. Int J Radiat Oncol Biol Phys 1980; 6:349–352.

18- Eden BV, Debo RF, Larner JM, et al. Esthesioneuroblastoma; long term outcome and patterns of failure-the University of Virginia experience. Cancer 1994; 73:2556–2562.

19- Beitler JJ, Fass DE, Brenner HA, et al. Esthesioneuroblastoma: is there a role for elective neck treatment? Head Neck 1991; 13:321–326.

20- Morita A, Ebersold MJ, Olsen KD, Foote RL, Lewis JE, Quast LM. Esthesioneuroblastoma: prognosis and management. Neurosurgery 1993; 32:706–715.

21- Davis RE, Weissier MC. Esthesioneuroblastoma and neck metastasis. Head Neck 1992; 14:477–482.

22- Dulguerov P,Abdolkarim SA. Esthesioneuroblastoma a meta-analysis and revew. The Lancet oncology 2002; 2:683-690.

23- Ozcan C,Ergin TN.Endoscopic removal of Esthesioneuroblastoma.J ped Otorinolaryn -gology 2002; 64 :233-238.

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خلاصه

استزیونوروبلاستوما

دکتر محمد فرجی، دکتر محمد نعیمی

مقدمه : هدف از این مقاله بررسی بیماران مبتلا به استیزیونوروبلاستوما در بیمارستان قائم از ۱۹۹۰ تا ۲۰۰۴ با درنظر گرفتن یافته های بالینی، مطالعات رادیولوژیکی، درجه بندی تقسیم بندی هیستوپاتولوژیکی و پیش آگهی آن می باشد.

روش کار : برای این مطالعه پرونده بیماران با تشخیص استیزیونوربلاستوما در بخش های جراحی اعصاب و گوش و گلو و بینی و پاتولوژی بررسی شد. بیمارانی در مطالعه قرار گرفته که نمونه پاتولوژی آنها در دسترس بود در مجموع ۱۳ بیمار وجود داشت یک بیمار به علت به اثبات نرسیدن نمونه پاتولوژی کنار گذاشته شد و ۱۲ بیمارمورد بررسی قرار گرفت. استریونوروبلاستوما تومور بدخیم نوروانداوکرینی است که از بافت مخاط بویایی ایجاد می شود و از سلول های آبی رنگ کوچک که ساختمان لوبولر به خود می گیرد تشکیل می شود. در این بررسی تومورها براساس درجه بندی کادیش تقسیم بندی شده و برای بررسی پیش آگهی از بررسی میزان بقاء کاپلان مایر نیز استفاده شده است.

نتیجه گیری : درجه بندی کادیش برای بررسی پیش آگهی بیماران توانایی کافی را دارد و انتشار تومور به داخل جمجمه، وجود متاستاز موقع تشخیص بیماری، از فاکتورهای موثر در پیش آگهی بیمار می باشد.

واژه های کلیدی : استیزیونوروبلاستوما، هیستوپاتولوژی، بررسی میزان بقاء، ایمنوهیستوپاتولوژی.