Olfactory esthesioneuroblastoma

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Neurogenous tumours of the nasal cavity and nasal sinuses make up 3 per cent of the true neoplasms in this area (Becker and Jacox, 1964; McCormack and Harris, 1955).

These tumours are due to three anatomical factors: the close relation (1) to the central nervous system, (2) to the peripheral nerves and ganglia, and (3) to the olfactory region.

Owing to the rare occurrence of tumours of olfactory derivation and their frequently motley morphology, divergent data are still being published about their histogenesis, histopathology, prognosis, and the therapeutic principle.

We feel it must be relevant to contribute our experience of 3 cases diagnosed and treated during the period 1961–1971. The clinical course of all three cases is given in brief outline in Table I. One of the cases (Case 1) has previously been published by Kolze (1968).

TABLE I.
SCHEMATIC HISTORIES OF THREE PATIENTS WITH ESTHESIONEUROBLASTOMA

	Case 1	Case 2	Case 3
Age and sex	68-year-old woman	56-year-old woman	25-year-old man
Main symptoms	Nasal obstruction, frontal headache	Nasal obstruction	Epistaxis
Duration	6 months	6 months	9 months
Signs	Greyish tumour filling the entire nasal cavity. Exophthalmos.	Papillomatous swelling of the right inferior concha.	Red granulating tumour in the right nasal cavity. Exophthalmos.
X-ray findings	Bone destruction.	Blurring of nasal sinuses. Bone destruction.	Calcification of the tumour. Bone destruction. Blurring.
Treatment	Radiotherapy	Radiotherapy +surgery.	Radiotherapy +surgery
Results	Primary regression. Subsequent progression + metastases in lymph nodes. Died after 3 years.	Alive without recurrence after 12 years.	Alive without recurrence after 7 years.

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Histogenesis

The primordium of the olfactory apparatus is present in the late somite embryo (5 mm. stage) as the olfactory placodes. From this stem epithelium—the esthesioneuroblastoma—the supporting and nervous epithelium is differentiated from the olfactory region (Hamilton, Boyd and Mossman, 1972).

Tumours derived from the olfactory epithelium—esthesioneuroblastomas—are characterized (Fig. 1) by (1) the nerve cell, either as the undifferentiated neuroblast or the differentiated neurocyte, (2) occurrence of neurofibrils, and (3) more variably by the sporadic cellular arrangement into true neuroepithelial rosettes and so-called pseudo-rosettes (Hutter *et al.*, 1963, Kahn, 1974). Of these characteristics the occurrence of neurofibrils is said to be diagnostic in the light microscope (Kahn, 1974; Obert *et al.*, 1960).

It has previously been assumed that it was the supporting cell which formed the true rosettes, but according to electron microscopic studies the rosettes are made up of neurogenous cells, imitating a primitive neural tube (McGavran, 1970; Kahn, 1974).

Olfactory tumours have been divided into three sub-groups: (1) esthesioneuroblastoma characterized by the undifferentiated olfactory cell, (2) esthesioneurocytoma characterized by the differentiated olfactory cell, and (3) esthesioneuroepithelioma characterized by the differentiated olfactory cell as well as the differentiated supporting cell. However, in most tumours—including those of our own material—all components are present, and as electron microscopic studies have shown them to be purely neurogenous tumours (McGavran, 1970; Kahn, 1974), there seems to be no reason to maintain this subdivision.

Incidence

Since Berger *et al.*, in 1924, described the first case of esthesioneuroblastoma, a total of 130 cases have been reported up to 1972 (Schenck and Ogura, 1972). In the past few decades the incidence seems to have been rising, but this is more probably due to better differential diagnosis than to a real increase in the number (Skolnik *et al.*, 1966; Obert *et al.*, 1960; Frühling and Wild, 1954; Fisher, 1954).

Age and Sex

Esthesioneuroblastomas occur in all age groups. They have been reported at ages from 8 to 79 years, distributed equally in all decades, but possibly with a peak incidence in the second (Lewis *et al.*, 1965) thus differing from the sympathiconeuroblastoma which has a peak incidence during infancy. Our youngest patient was 25 and the oldest 68.

The tumour appears to be equally common in males and females

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(Fitz-Hugh *et al.*, 1965; Seaman, 1951; Mendeloff, 1975; Fisher, 1954). However, MacComb *et al.* (1967) found a male preponderance of 2:1.

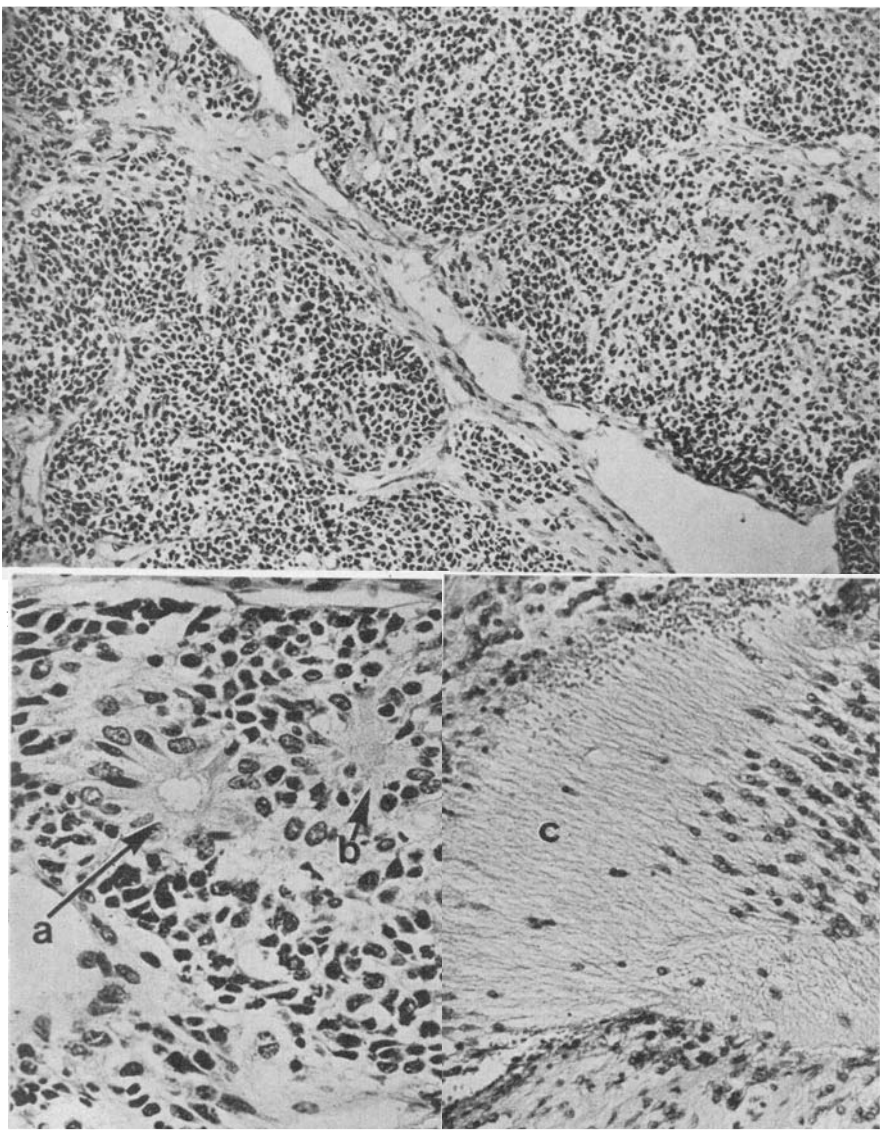


FIG. 1.

Microphotograph showing: (1) a general view of esthesioneuroblastoma and (2) the different diagnostic features in: (a) true rosette, (b) pseudorosette, (c) neurofibrils.

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Diagnosis and Differential Diagnosis

With regard to symptoms esthesioneuroblastoma does not differ from other tumours of the same site. Unilateral nasal stenosis lasting for months and recurrent haemorrhage are the most common ones. Unilateral frontal headache and anosmia are less common (Lewis *et al.*, 1965).

The signs are also not characteristic. As a rule there will be a greyish red, oedematous, polypoid, readily bleeding tumour, localized in most cases superoposteriorly in the nasal cavity.

Some of the patients have been subjected to repeated removal of nasal polyps which have not primarily been examined microscopically. This emphasizes that the differential diagnosis from benign nasal polyp cannot be made grossly (Obert *et al.*, 1960; Mendeloff, 1957; Schenk and Ogura, 1972; Lewis *et al.*, 1965).

If the tumour is predominated by the undifferentiated esthesioneuroblast there may be differential diagnostic difficulties against other poorly differentiated tumours, such as plasmocytoma, malignant melanoma, and especially malignant lymphoma and small-cell anaplastic carcinoma (Skolnik *et al.*, 1966; Obert *et al.*, 1960; Frühling and Wild; 1954, Fisher, 1954).

Against sympathiconeuroblastoma an unchanged urinary excretion of 3-methoxy, 4-hydroxy-mandelic acid is of differential diagnostic value (Kolze, 1968).

X-rays show in characteristic cases unilateral blurring of the maxillary antrum and ethmoid cell, whereas bone destruction is said to be rare (Frühling and Wild, 1954; Becker and Jacox, 1964; Lewis *et al.*, 1965; Joachims *et al.*, 1975). All our cases exhibited bone destruction. In our opinion, this must be expected in a large number of these cases, as the tumour is a malignant one. However, the destruction is presumably often demonstrable only by tomographic views of the nasal sinuses.

A few of the published cases, like our Case 3, have had calcification of the tumour (Mendeloff, 1957; Schenck and Ogura, 1972), but this can hardly be attributed with any importance *per se*. Radiological changes characteristic of this tumour cannot be expected (Fitz-Hugh *et al.*, 1965; Psenner, 1963).

Histopathology and Prognosis

Several authors have tried to correlate the histological appearances with the degree of malignancy and tendency to metastasize.

McCormack and Harris (1955) divided tumours of olfactory derivation into a malignant form characterized by the presence of true rosettes and/or pseudorosettes (neuroepithelioma and neuroblastoma respectively) and a benign form in which neither rosettes nor pseudorosettes are demonstrable (neurocytoma).

Mendeloff (1957) reported that tumours characterized by the presence

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of pseudorosettes (type I) were apt to metastasize, while those characterized by true rosettes (type II) merely showed invasive growth.

It has been maintained by Obert *et al.* (1960) that tumours with true rosettes do not only run a more rapid course, but also metastasize.

Table II gives the histological findings in our three cases. All exhibited neuroblasts, neurocytes, and fibrillar matter. Case 1 soon developed regional lymph node metastases and the patient died 3 years after primary admission. In this case the tumour was predominated by neuroblasts and otherwise characterized by aggressive growth, numerous mitoses, and a few rosettes. In Case 2 there have been no metastases or signs of recurrence, and the patient is alive and well 7 years after primary admission. Case 3 has never exhibited metastases or signs of recurrence. She is alive 12 years after primary admission. In the last two cases the tumour was more highly differentiated and had but few mitoses.

TABLE II.

HISTOPATHOLOGICAL FINDINGS IN THREE CASES OF ESTHESIONEUROBLASTOMA

	Case 1	Case 2	Case 3
Neuroblasts	+++	+	++
Neurocytes	++	+++	++
Neurofibrils	(+)	+++	+
Pseudorosettes	++	o	++
True rosettes	+	o	o
Mitoses	+++	+	(+)

Our small series appears to show that the general degree of differentiation and the number of mitoses are the main factors of prognostic significance. In this respect, the presence of rosettes and pseudorosettes seems to be of minor importance.

Treatment

Where treatment is concerned, too, different views apply, especially with regard to radiosensitivity. According to Mendeloff (1957) these tumours are highly radiosensitive, whereas Lewis *et al.* (1965) and Fitz-Hugh *et al.* (1965) have found a wide variation in radiosensitivity. Skolnik *et al.* (1966), reviewing 97 cases, found a 5-year survival of 64 per cent after surgery alone and of 38 per cent after radiotherapy alone. On combined treatment throughout the course the survival rate was 50 per cent. They advised surgical treatment, reserving radiotherapy for recurrences, if any.

In our first patient there was but a moderate effect of radiotherapy on the primary tumour, but apparently somewhat better upon the regional lymph node metastases. Supplementary surgery was not attempted because of the extensive spread of the tumour. The other two patients had combined treatment, viz. primary radiotherapy in a full tumour

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dose, followed by surgical excision. In one (Case 2) radiotherapy had a good effect, in the other (Case 3) no definite effect. These two patients are alive without recurrence or metastases 12 and 7 years respectively after the treatment was completed. We, therefore, advise combined treatment, viz. irradiation in a full tumour dose followed by operation.

Summary

Esthesioneuroblastomas are malignant tumours, usually of slow, invasive growth and low metastatic rate. Skeletal destruction must be assumed to be common, but is often demonstrable only by tomographic sections.

Clinically these tumours do not differ from others of the same site, so that the diagnosis has to be based upon the histological appearances. In the light microscope the presence of neurofibrils is considered a specific differential diagnostic factor against other small-cell malignant tumours in this region.

There seems to be no basis for a morphological classification into previously described sub-groups, neither according to histogenetic, light, nor ultra-microscopic findings. The general degree of differentiation and the number of mitoses appear to be the main factors of prognostic significance.

Combined irradiation and surgical excision is considered the best treatment.

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