University of Toronto Combined Neurosciences Rounds

Rhabdomyosarcoma of the Head and Neck in Children

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Case Report (Dr. Humphreys)

Rhabdomyosarcoma of the head and neck region in children frequently presents with otolaryngologic symptoms. But tumours which arise along the cranial base and involve the middle ear, mastoid or nasopharynx may be associated with specific neurological phenomena (Fleischer et al., 1975). The following case illustrates these points. It also records the unusual development of remote, intradural metastatic disease. Rhabdomyosarcoma rarely gains access to the subarachnoid space. When it does, the route of penetration is usually directly from ear through internal auditory meatus to cerebellopontine angle (Russell and Rubinstein, 1970). Our case developed a metastatic intradural spinal lesion without interposed disease.

An 18 month old infant presented with sudden onset of a painless left 6th nerve palsy. There was no history of recent trauma or infection, and the neurological and general examination was unremarkable except for complete failure of abduction of the left eye. The CT axial cuts of the brain were normal. Three days later the child developed a completely "frozen" left eye. This was characterized by ptosis, a slightly larger pupil which reacted sluggishly to direct light stimulation, and complete immobility of the globe. The fundas was normal.

The original skull x-rays were reviewed and revealed marked erosion and enlargement of the left foramen ovale. Coronal cuts on computed tomography showed an enhancing lesion arising extracranial on the infratemporal surface of the skull and extending up through skull base into the intracranial extradural compartment. Subsequent carotid arteriography outlined a vague mass in the pterygoid fossa.

An attempt was made to biopsy the mass via the nasopharyngeal route, but the yield was not confirmatory. When it was determined that the tumour could not be approached transorbitally, the left middle fossa was explored.

1st. Operation.

The mass was approached along the anterior extremity of the floor of the left middle fossa. It had expanded the foramen ovale and stretched the mandibular portion of the trigeminal nerve. The foramen was surgically enlarged and the hard, rubbery mass was easily dissected from the overlying dura mater which it had indented. The tumour was entirely extradural. The capsule of the tumour was broached, and whitish tissue removed for biopsy. On the basis of the quick-section examination, nothing further was done at that time.

The diagnosis of rhabdomyosarcoma was confirmed and the child received radiation therapy to the involved area of the skull base to a total dose of 5,000 rads. She also received Vincristine, Actinomycin-D, Adriamycin, Cyclophosphamide and intrathecal Methotrexate. She had no complications over the next 10 months.

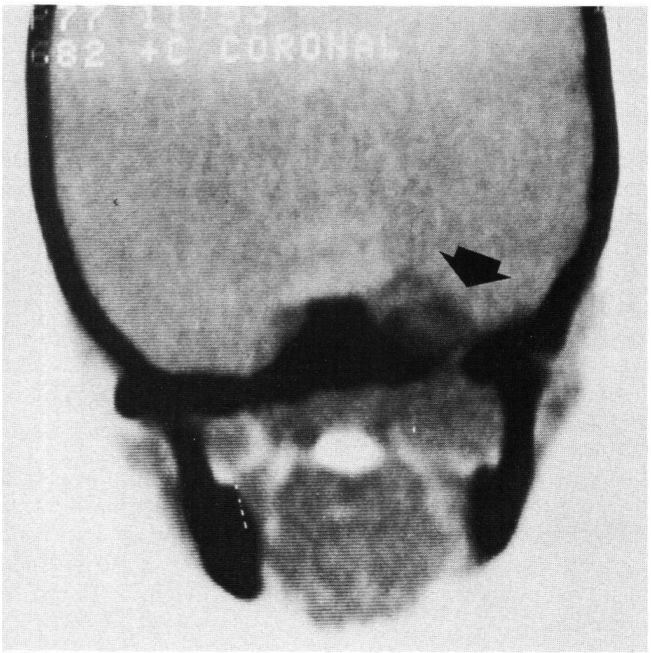

Figure 1 — Coronal CT Scan showing an enhancing lesion which has penetrated through the base of the skull into the intracranial extradural compartment.

She was readmitted to hospital 11 months following the original diagnosis because of irritability, fussiness at night and progressive deterioration of gait over the preceding 48 hours and this progressed to flaccid paresis of the entire right leg. The myelogram showed a complete block at T3-4. The CSF protein was 649 mg. percent, and tumour cells, resembling those of the original neoplasm, were isolated on cytologic examination of the CSF.

2nd. Operation.

A laminectomy was performed at the T1-T3 level but this did not reveal the expected extradural tumour but the dura was tense. When it was opened longitudinally a discrete 5 cm. long torpedo-shaped tumour was seen lying to the right and dorsal to the midline of the spinal cord. The cord was severely compressed. At the upper and lower poles the tumour had a plane of cleavage, but in between it was impacted into cord substance. It surrounded emerging thoracic roots. A major, but subtotal excision of this partially intramedullary tumour was achieved.

After this operation, the patient received a total of 4500 rads to the thoracic spine and an additional 2500 rads to the skull.

The radiation program was completed six weeks following the spinal surgery, but the chemotherapy routine continued. She was well for six

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weeks but then was readmitted to Princess Margaret Hospital in a terminal state with signs suggestive of bulbar failure. She died two weeks later.

DISCUSSION

Clinical Features (Dr. McGreal)

Dr. J. McMenimin has reviewed the case records of 103 patients admitted to the Hospital for Sick Children between 1935 and 1979 in whom a diagnosis of rhabdomyosarcoma was made. It is his figures which are reported here. Of the 103 cases, 16 involved the head and neck and presented with neurological signs. There were 14 males and 2 females, with an age range from birth to 12 years. The distribution of tumour origin was: middle ear cleft 10, nasopharynx 3, paraspinal 3.

Middle ear cleft. The most common presentation was a peripheral facial paralysis which occurred in 9 patients. In 5 cases this was the only nerve involved when the patients were first seen. Of the patients who could be tested for hearing there were 5 with clinical deafness on the same side as the facial palsy, 3 sensorineural and 2 conductive. The interval from the onset of symptoms until the correct diagnosis was made ranged from 2 weeks to 3 months. The signs were variously interpreted as due to otitis media, mastoiditis or an inflammatory mass.

Nasopharynx. All three patients had multiple ipsilateral cranial nerve lesions. In addition, an orbital apex syndrome was present in one patient, with decreased acuity and optic atrophy due to infiltration of the optic nerve. Paroxysmal facial pain in one patient was initially thought to be due to petrositis.

Paraspinal. The symptoms and signs of root and cord compression varied according to the size and site of the mass. Horner's syndrome was present in one case.

Special Investigations.

The most reliable investigation was the CT scan. Of 7 patients in whom this examination was performed, the tumour was demonstrated in 5. Plain films of the skull were abnormal in 4 out of 9, but when special views of the mastoid area were combined with tomography of the skull base abnormalities were seen in 10 of 11 patients. Usually this took the form of erosion of the base. Electroencephalography was abnormal in 3 of 4 patients with intracranial extension of tumour.

Pathology.

Thirteen tumours were embryonal and three were alveolar.

Radiological Aspects (Dr. Fitz)

Before the availability of CT scanning, radiological evaluation of rhabdomyosarcoma of the face and skull base was confined to plain films, conventional tomography, and angiography of pneumoencephalography for definition of the extent of the tumour. Tomography was useful in defining bony destruction. Angiography was helpful to visualize soft tissue masses. If the mass was vascular, the soft tissue extent and intracranial spread were fairly clearly seen (Archer, 1976).

CT has made the radiological investigation of rhabdomyosarcoma more refined and is the most accurate method of defining tumour extent, metastasis, and recurrence in both bone and soft tissue. The use of CT has probably allowed earlier diagnosis and helped to make treatment more accurate. With the use of CT, large intracranial extension of tumour as reported by Harwood-Nash (1971) has not been seen at the Toronto Hospital for Sick Children. Spread to the extradural compartment has remained common.

Since CT became available, we have examined 16 primary rhabdomyosarcomas of the face and skull base. Of these only one, a small tumour of the soft palate, was not visible on CT. The patients varied in age from two months to 11 years with a mean of four years, 14 of the 16 being under seven years old.

The petrous bone (8 cases) was the most common single primary site. Erosion of the petrous bone or skull base is often visible on plain film, but CT is far better in evaluating the extent of destruction. The most significant feature of six primary petrosal tumours was spread into the extradural compartment. Two spread to both the middle and posterior fossae, four to the middle fossa only. Two of those involving the middle fossa extended into the pterygoid region and one went to the nasopharynx.

Though bony erosion of the skull base on CT or skull x-ray raises the suspicion of intracranial involvement, the actual extradural component is often seen best only after intravenous contrast and in the coronal projection (Fig. 2). The well circumscribed borders of the tumour suggest a lack of brain invasion on CT, but angiography remains a useful confirmation of this as an intradural spread may have abnormal vascularity.

In addition to the six tumours arising from the petrous region, one from the pterygoid fossa itself and another large tumour from the face extended intracranially. Both of these were also spread into the extradural portion of the fossa.

Six tumours arose from the face anterior to the pterygoid fossa. They were variable in their radiological extent. Of four orbital tumours, only one was confined to the orbit, and the others involved adjacent structures. In total, the nose was involved in three, the nasopharynx in four (including one arising in the petrous bone), the ethmoid sinus in one, the maxillary sinus in three, and the sphenoid sinus in two. The tumour generally, but not always (Fig. 3), eroded bone to spread between compartments. Some contrast enhancement was noted in facial tumours, but it cannot be described as specific. Its extent and the fact that rhabdomyosarcoma is the most common primary tumour in this region are of more diagnostic value.

The tumour may be totally avascular with only a small displacement effect at angiography, or it may have a blush and abnormal tumour vascularity (Fig. 4). The role of angiography depends on the treatment planned, and is of most value in total excision. Knowledge of the vascular supply of the tumour can be helpful during operation.

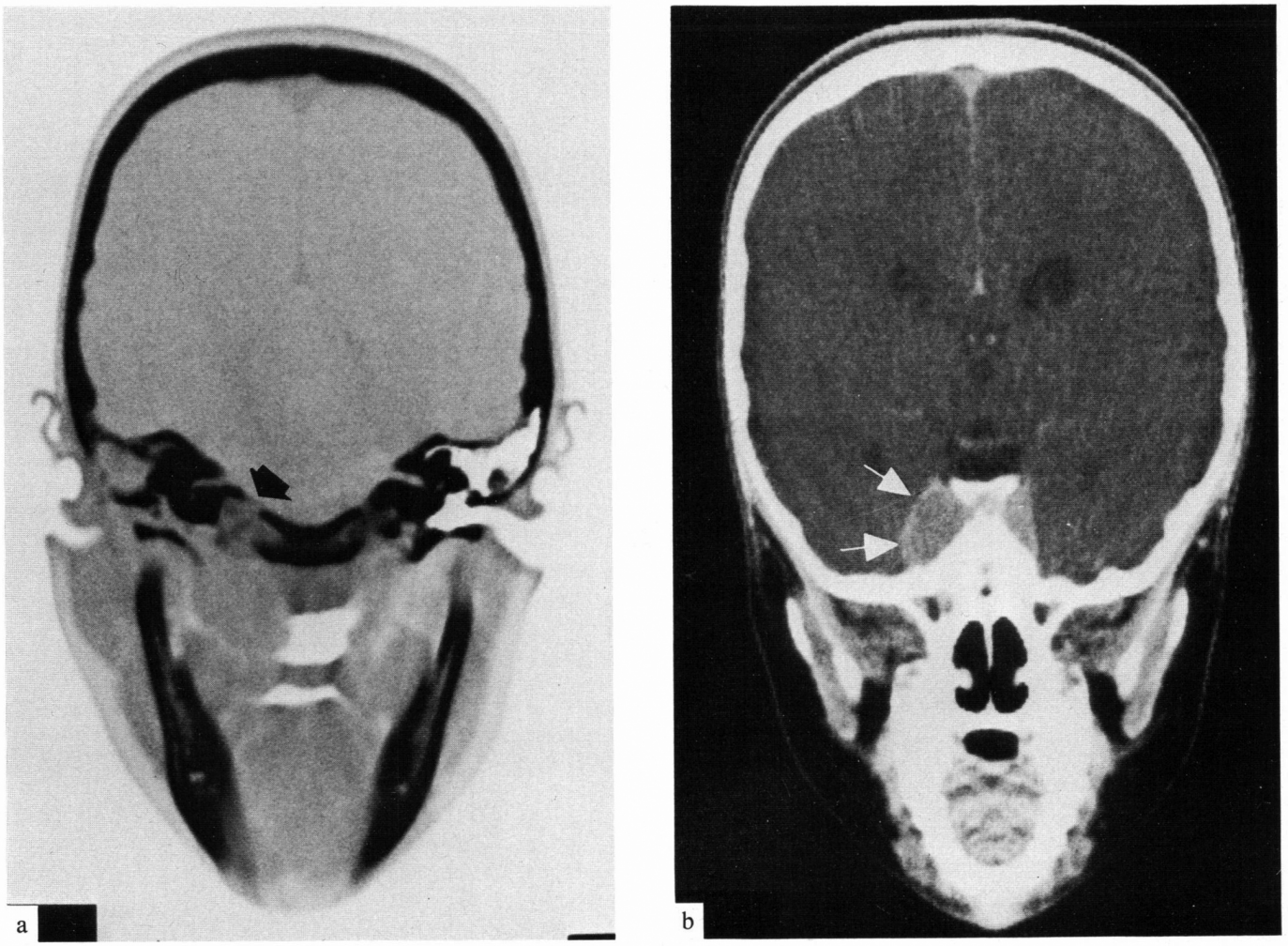

Figure 2 — Bone and Extradural Invasion. (a) Coronal view, reverse gray scale, shows soft tissue density throughout the middle and external ear and mastoid air cells. Erosion of the clivus is present (arrow) and a soft tissue mass can be seen in the right side of the nasopharynx beneath it. (b) More anterior coronal view reveals tumour involving the cavernous sinus region with resultant mass effect (arrows).

Pathology (Dr. Becker)

Rhabdomyosarcoma usually occurs in childhood, although it may present at any age (Masson and Soule, 1965). Of the head and neck tumors, about 80% occur in children under the age of 12 years and 55% under the age of 5 years. Of the 170 cases which Dito and Batsakis (1962) reviewed, 31.6% occurred in the orbit and eyelids, 23.6% in the neck, face, and temporal region, 28.8% in the nasopharynx, tongue, palate, uvula, hypopharynx, tonsil, floor of the mouth, and gingiva, 8.8% in the ear, mastoid, and maxillary sinus, and 7.2% were found in the mandibular, salivary gland, and occipital regions.

A recent report of the Intergroup Rhabdomyosarcoma Study described 202 patients with rhabdomyosarcoma of the head and neck (Sutow et al, 1982). Forty-six percent were in parameningeal sites. The term "parameningeal" was used to include those sites anatomically adjacent to the meninges. Specifically, they included middle ear, mastoid, ear canal, nasal cavity, paranasal sinus, nasopharynx and infratemporal fossa.

Horn and Enterline (1958) have subclassified rhabdomyosarcoma into essentially three types: embryonal-botryoid, alveolar, and pleomorphic. Histologically, the most common variety of rhabdomyosarcoma of the head and neck is the embryonal or botryoid form depending on whether or not the tumor is associated with a mucous membrane surface. Sutow et al. found 78% were embryonal-botryoid, 9% alveolar, 10% undifferentiated, and 3% extraosseous Ewing's types. Of the 16 cases discussed by Dr. McGreal, 13 are embryonal and 3 alveolar. The pleomorphic rhabdomyosarcoma occurs almost exclusively in adults. In the oral region, rhabdomyosarcomas of the tongue are of the pleomorphic type.

The basic cell type of the embryonal rhabdomyosarcoma is a long, spindle-shaped cell with a single nucleus and eosinophilic cytoplasm. Longitudinal and/or cross striations may be seen in these cells but usually they are difficult to identify. Some cells may be larger and oval-shaped with abundant, bright, eosinophilic cytoplasm, or the cells may be undifferentiated with round nuclei and little cytoplasm (Fig. 5). The botryoid rhabdomyosarcoma differs from the embryonal variant only in its location and gross appearance. The grape-like lesions of the botryoid rhabdomyosarcoma are histologically edematous and relatively acellular. They are covered by a normal mucous membrane,

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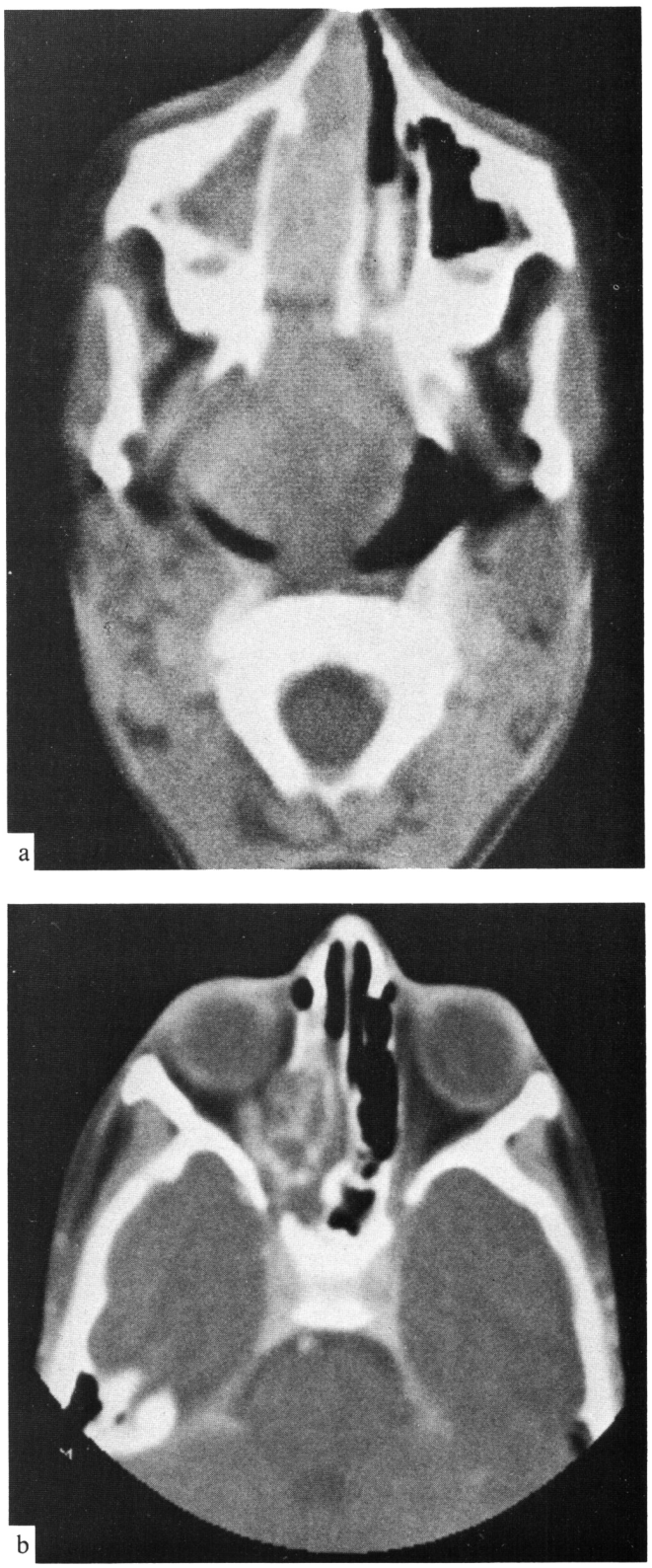

Figure 3 — Large Facial Tumour. (a) Axial CT through the zygomatic region reveals tumour in the nasal passage with expansion and destruction on the right side. The tumour extends as a huge mass into the nasopharynx with erosion of the medial side of the pterygoid plate. Tumour has invaded the right antrum without bony destruction. (b) Higher slice through the orbits shows invasion and destruction of the ethmoid and sphenoid sinuses, and expansion into the posterior right orbit.

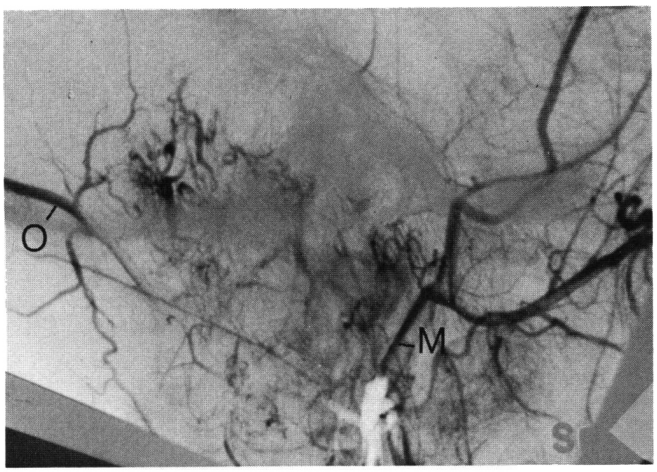

Figure 4 — Angiography. Lateral view of a selective external carotid arteriogram shows abnormal tumour blush (arrows) outlining the extra-cranial retro-mastoid portion of the tumour. O = occipital artery; M = maxillary artery.

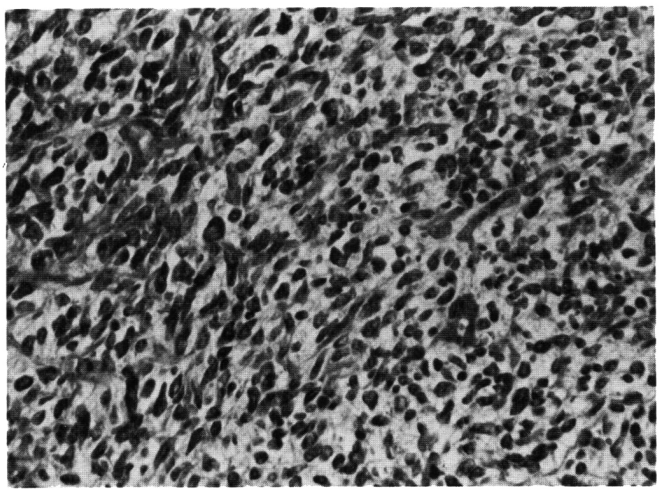

Figure 5 — Embryonal rhabdomyosarcoma with poorly differentiated spindle cells. Hematoxylin and eosin, X400.

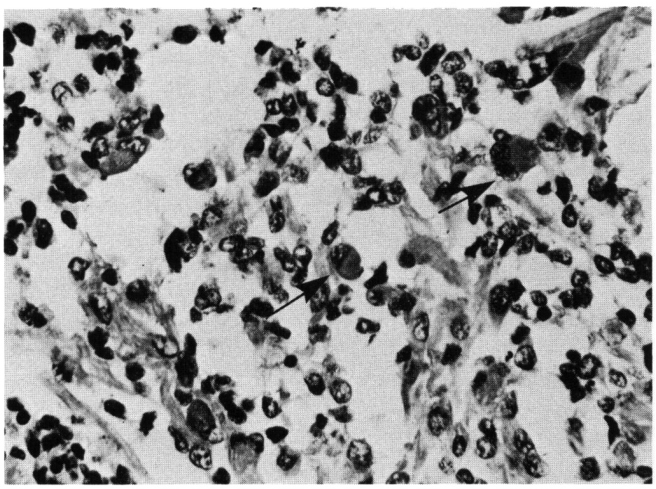

Figure 6 — Embryonal rhabdomyosarcoma with focal positivity (arrows) with antiserum to adenosine triphosphatase. Immunoperoxidase, X400.

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but beneath the epithelium is the characteristic multilayered band of cells. These cells are oval to spindle-shaped, with little cytoplasm, and tend to lie parallel to the surface of the epithelium. Although the cells appear uniform, they have a high rate of mitotic activity. The histological similarity of the embryonal and botryoid rhabdomyosarcoma suggests they should be treated as a single group, the embryonal-botryoid rhabdomyosarcoma.

The alveolar rhabdomyosarcoma is characterized by alveoli which are separated by connective tissue trabeculae. One or more layers of the cells are usually closely applied to the trabeculae; but the centre may appear empty except for a varying number of unattached cells. Some of these cells may be multinucleated. Striations may occasionally be identified in these giant cells.

Pleomorphic rhabdomyosarcoma is a spindle-cell tumor of adults characterized by bizarre, pleomorphic, giant cells with abundant eosinophilic cytoplasm. Longitudinal and cross striations can often be identified.

Local recurrence and distant metastases are both common. The most frequent sites of metastases are lungs, lymph nodes, and bones. Other organs less frequently involved are heart, liver, kidney, testis, ovary and adrenal. Head and neck tumors tend to invade meninges and, in some series, meningeal involvement is as high as 35% (Tefft, 1978).

Both electron microscopy (Morales et al., 1972) and immunohistochemistry (Koh and Johnson, 1980) may be of diagnostic value. Kahn et al. (1982) studied 65 cases of childhood rhabdomyosarcomas. Twenty-five percent (16 cases) showed cross striations by light microscopy and about the same percentage showed definite skeletal muscle differentiation by electron microscopy. Positive immunohistochemical staining using antisera against myoglobin was demonstrated in 37%. When antisera against MM iso-enzyme of creatine kinase was also used, positivity was increased to 60%. Antisera against desmin, ATPase and calsequestrin were also useful (Fig. 6). This study suggests that immunoperoxidase techniques documenting the presence of markers of muscle differentiation may be of diagnostic use in childhood rhabdomyosarcoma.

Oncology (Dr. Gribbin)

Rhabdomyosarcoma represents 10-15% of solid tumours in childhood. The incidence peaks in the 2-6 year age group and then again in the teens. Head and neck rhabdomyosarcoma occurs more commonly in the younger age group than in the teenage years.

Rhabdomyosarcoma may arise wherever striatcd muscle is found. Primary head and neck rhabdomyosarcoma accounts for more than a third of all childhood cases. Maurer (1981) reported the distribution of sites among patients less than 20 years old, who were entered in the Intergroup Rhabdomyosarcoma Study from 1972 to 1976 (Table 1).

The Intergroup Rhabdomyosarcoma Study has a clinical grouping classification, which has been found to affect prognosis (Table 2). By the time diagnosis is established most cases of head and neck rhabdomyosarcoma are in Group III, with extensive local disease (Sutow et al., 1982). The initially painless growth of tumour spreads along

Table 1: Primary site of rhabdomyosarcoma in 554 patients (from Maurer, 1981)

SITE	PERCENT
Orbit	10
Other head and neck	28
Trunk	7
Extremities	18
Genitourinary	21
Intrathoracic	3
Gastrointestinal and hepatic	3
Perineum - anus	2
Retroperitoneum	7
Other	1
Total	100

Table 2: Clinical grouping classification (from Maurer, 1981)

GROUP	CLASSIFICATION
I	*Localized disease, completely resected* (regional nodes not involved) Confined to muscle or organ of origin Contiguous involvement with infiltration outside the muscle or organ of origin, as through fascial planes
II	*Grossly resected tumour with microscopic residual disease* No evidence of gross residual tumor. No evidence of regional node involvement Regional disease, completely resected (regional nodes involved and/or extension of tumor into an adjacent organ); all tumor completely resected with no microscopic residual tumor Regional disease with involved nodes, grossly resected, but with evidence of microscopic residual disease
III	*Incomplete resection or biopsy with gross residual disease*
IV	*Distant metastatic disease present at onset* (lung, liver, bones, bone marrow, brain and distant muscle and nodes)

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Table 3: Primary site of rhabdomyosarcoma and incidence of distant metastases at diagnosis and during treatment (from Okamura et al., 1977)

SITE	AT DIAGNOSIS*	DURING TREATMENT*	TOTAL*(%)
Orbit	1/20	5/19	6/20 (30)
Other head and neck	7/70	26/63	33/70 (47)
Trunk	4/18	5/14	9/18 (50)
Extremity	10/22	8/12	18/22 (82)
Genitourinary	5/24	8/19	13/24 (54)
Retroperitoneum	1/4	0/3	—
Unknown	3/3	—	—

* Number of cases with distant metastases/Total number of cases

Table 4: Management of childhood rhabdomyosarcoma

A Assess extent of primary tumour
B Investigate for metastatic disease
C Treatment for localized disease —
  1 Surgery: complete resection unless unacceptable functional or cosmetic effect
  2 *Combination chemotherapy: vincristine, cyclophosphamide and* actinomycin D +/- adriamycin
  3 Radiation therapy if any microscopic or gross residual tumour, to primary site with adequate margins. Dose: 4500-5000 rads in 23-25 fractions given five days a week
  4 Follow-up

physiological planes in the pharynx and base of skull. Further growth erodes bone, and cranial nerve palsies occur due to compression. Tumours arising in sites adjacent to the meninges, such as in the nasopharynx, middle ear and paranasal sinuses, are called parameningeal tumours. (Tefft et al., 1978). Sutow et al. (1982) found that of 93 cases of parameningeal rhabdomyosarcoma, 73% were in Group III and 16% were in Group IV. This can be compared with 43% of the 554 cases of rhabdomyosarcoma at all sites in Group III and 20% in Group IV (Maurer, 1981).

Embryonal rhabdomyosarcoma is the most common histological subtype in childhood. Sutow et al, reports that 75% of their cases of head and neck rhabdomyosarcoma were of this subtype. A higher incidence of metastatic disease occurs among children with alveolar rather than embryonal or the rare pleomorphic rhabdomyosarcoma (Okamura et al., 1977).

The incidence of distant metastases in association with head and neck rhabdomyosarcoma is similar to that at most other sites (Table 3), (Okamura et al. 1977). Orbital rhabdomyosarcoma has a low incidence of metastatic disease.

Spread of rhabdomyosarcoma to regional lymph nodes is unrelated to tumour size or histological subtype. Lymph node involvement is not common when the patient is first seen (Lawrence et al., 1977).

The approach to the management of childhood rhabdomyosarcoma is shown in Table 4.

Diagnosis is made from histological examination of a biopsy after full clinical examination and radiological assessment of the primary site. Possible metastatic disease is looked for by radiological and radio-isotope scans of the lungs, skeleton and liver and by bone marrow aspirate. If the primary site is parameningeal, the cerebrospinal fluid may contain malignant cells.

For children with localized disease a complete surgical resection, with histologically clear margins, should be attempted. If the tumour cannot be completely excised then a radical course of radiation therapy is given. In a child this can result in radiation-induced morbidity. After radiation therapy for head and neck rhabdomyosarcoma facial growth may be asymmetrical and normal dentition may be disturbed (Nwoka et al., 1975). Radiation-induced pituitary damage can result in deficiencies of growth hormone, thyroid stimulating hormone and gonadotrophins, which will require replacement therapy (Fuks et al., 1976). Direct or scattered radiation therapy to the thyroid gland can give rise to delayed hypothyroidism and thyroid malignancy (Modan et al, 1974).

Thus treatment should be planned co-operatively by pediatric oncologist and radiation oncologist. The risk of functional and cosmetic impairment from treatment must be balanced against the expectation of local control of the disease.

Combination chemotherapy is used in all cases of rhabdomyosarcoma for improved local control and prevention of metastatic disease. Increased survival has resulted from the combined use of the first three drugs listed in Table 4C(2). The possible additional benefit of adriamycin is being studied. Children are at risk from the usual acute side effects of chemotherapy and secondary immunosuppression. Severe oral and pharyngeal mucosal reactions can occur during radiation therapy to these areas when chemotherapy is administered concurrently.

Radiation therapy is used in most cases. Advanced radiological imaging, including computerized tomography, assists in planning radiation fields. A margin of healthy tissue around the tumour site must be treated (Tefft et al., 1981). We believe that if adequate margins are treated no

advantage is gained by treatment of the craniospinal axis in parameningeal rhabdomyosarcoma (Berry and Jenkin, 1981).

Acute side effects and deformity due to growth impairment are more likely with higher doses of radiation therapy. Jereb et al. (1980) recommend moderate doses of radiation but with intensive combination chemotherapy for the treatment of embryonal rhabdomyosarcoma. Follow-up examination should concentrate on the primary and possible metastatic sites for recurrent disease and on the recognition of treatment-induced complications. Consultations from plastic and dental surgeons and pediatric endocrinologists may be required. The patients are at risk for a second malignancy, due to natural but unexplained susceptibility and to the additional oncogenic effects of radiation and chemotherapy.

One hundred and three patients with head and neck rhabdomyosarcoma who had no distant metastases at diagnosis and were treated on the protocols of the Intergroup Rhabdomyosarcoma Study, have now been followed for three years. They received chemotherapy for two years. Most relapses occurred within the first two years from diagnosis; relapses occurring three years or more from diagnosis are rare (Pratt et al., 1981). Sutow et al. (1982) report a three-year relapse-free survival rate of 91% for tumour of the eye and orbit, 45% for parameningeal primaries and 75% for other sites in the head and neck. This represents a 66% three-year relapse-free survival rate for this group of patients with head and neck rhabdomyosarcoma.

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