Rhabdomyosarcoma of the Head and Neck in Children *

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Rhabdomyosarcoma of the head and neck in children is usually a relentless, progressive tumor which results in the death of a child in a relatively short time. The present report of seven cases is presented first to suggest that aggressive surgical attack may occasionally be rewarding and not mutilative and secondly that the use of anti-cancer chemotherapeutic agents may exert a beneficial effect upon survival.

Rhabdomyosarcoma is one of the more common soft tissue tumors in adults exceeded in incidence only by liposarcoma and fibrosarcoma. Stout [11] in 1946 delineated the features of this tumor and reported 107 cases, most of which were of the pleomorphic type. Other varieties were reported by Stobbe and Dargeon,[10] Riopelle and Theriault,[9] and Horn and Enterline.[4]

Pathology

The several varieties of rhabdomyosarcoma mimic the stages in development of striated muscle.[1] Most authors classify the varieties of rhabomyosarcoma as embryonal, alveolar, and pleomorphic. The first two of these represent early embryonal growth of striated muscle and usually do not show cross striations. The more mature pleomorphic variety usually exhibits striations. The rhabdomyosarcoma may represent different stages in growth of striated muscle and the myoblast may assume one or all of several shapes: round cell, racket-shaped cell, or strap-shaped cell.

The gross appearance of the rhabomyosarcoma is not characteristic except in the sarcoma botryoides variety of the embryonal type which presents as multiple grape-like mucinous structures. Other varieties vary in consistency from being quite hard to resembling lard. The gross appearance and particularly with variation in color is determined by the amount of invasion into adjacent structures and the necrosis of the tumor itself.

The embryonal type is usually a tumor of early childhood and is one likely to be found in the head and neck. It is the second most common variety to be found in the orbit.[4] Stobbe and Dargeon [10] describe this tumor as one with long spindle-shaped cells with an ovoid central single nucleus and acidophilic cytoplasm and bipolar cytoplasmic processes. These cells are occasionally called strap cells. Other cells are found to be round with scanty cytoplasm. Although they form parallel rows, there is no palisading of nuclei. The spindle cell resembles developing myoblasts as seen in embryos at seven to ten weeks of age.[5] The botryoid variant arises most often in visceral structures and is usually covered by an intact mucosa. The tumor is edematous and an abundance of tumor cells are found concentrated immediately beneath the mucous membrane. This variant has been reported in the maxillary sinus, middle ear, uterus, bladder, and the common bile duct.[6]

The alveolar type of rhabdomyosarcoma as described by Horn [4] and Riopelle [9] presents as multiple ovoid spaces lined by

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epithelial-like cells which are sparse and whose cytoplasm is continuous with the alveolar wall. Alveoli are separated by connective tissue trabeculae; some multinucleated giant cells and round cells are seen. Cross striations can generally be noted. This hollow tube pattern resembles developing muscle in the tenth to eleventh week of fetal life.[6] This tumor is most commonly encountered during adolescence.

The pleomorphic type is usually seen as a tumor of adults. It has a very cellular structure with scanty stroma and the cells are spindle-shaped and show no definite pattern of arrangement. Collagen is lacking. Large bizarre cells have nuclei occupying an expanded end of the cell and in so doing resemble a tadpole. Again cross striations are generally identifiable.

Many rhabdomyosarcomas show a mixed histopathologic picture and the Armed Forces Institute of Pathology classification[11] of varieties such as the embryonal-alveolar type is in common usage.

Rhabdomyosarcoma has been reported in patients varying in age from two weeks[4] to 72 years.[8] Malignant cells are apparently carried along muscle planes. Hemorrhage or tumor necrosis occurs and for this reason involved musculature should be excised whenever feasible from origin to insertion.[7]

Prognosis

The usual survival rates in these tumors are very disappointing, the average life span following diagnosis of pleomorphic and alveolar varieties being less than one year. In the embryonal variety survival may be as long as 15 months. Phelan[8] reports a 30 per cent three to five year survival and Pack[7] reports 34 per cent five-year survival following radical surgery. These two series are remarkable when compared with others with much higher mortality rates.

Horn and Enterline[4] report five out of 40 patients living more than three years and Grossi[3] has only three patients alive beyond three years postoperatively. Stout[11] in 1946 reported four out of 121 patients surviving for five years.

It seems that the embryonal variety is more amenable to therapy. Horn and Patton[5] indicated that four out of five of their cases with survival in excess of three years were of the embryonal type.

Case Reports

Case No. 1. D. S. A 2½-year-old white boy was admitted to The Children's Hospital of Philadelphia on 11/24/54 with left otalgia, otorrhea, and repeated bouts of pyrexia of two months' duration. This child had been treated for left hydronephrosis due to congenital ureteropelvic obstruction and at the time of admission still had a subacute urinary infection. Two weeks prior to admission some bleeding and discharge of friable tissue was noticed from the left ear.

Physical examination revealed a very restless, irritable child with a temperature of 37.4° C. There was diffuse swelling about the left mastoid region. Multiple polyps were noted in the left external auditory canal. Roentgenographic examination of the mastoids revealed no abnormality. The polyps were removed and the child was placed on antibiotics and was discharged from the hospital.

He continued to have otalgia and otorrhea and the swelling around the left mastoid progressively increased and some left facial weakness was evident. Roentgenographic studies done on readmission on 12/20/54 showed osseous destruction of the left mastoid process and radical mastoidectomy was performed. Histopathological examination demonstrated undifferentiated mesenchymal tissue containing round cells and spindle cells with central ovoid nuclei and biploar cytoplasmic processes. This was consistent with a diagnosis of embryonal rhabdomyosarcoma.

Two weeks later he developed fullness of the soft palate and a large tumor mass almost completely filling the nasopharynx and pressing forward upon the soft palate was observed. Radiation therapy was begun and within ten days there was definite regression of tumor with improvement in the airway. Radiation was completed in 24 days with a dose of 3,100 R. He then developed a purpuric lesion of the tongue, excessive sialorrhea, dysphagia, and pyrexia up to 39.4° C. The tumor had completely disappeared clinically, but the left ear was filled with muco-purulent material. On 8/25/55 he was re-admitted with a history

of headache, vomiting and left otorrhea, and expired within two days. Autopsy revealed complete replacement of left middle ear and the remaining osseous area around the mastoid with polypoid friable tumor. This tumor extended into the cranial fossa, causing internal hydrocephalus. Histopathological examination showed cells characterized by their pleomorphism, with prominent nuclei occupying expanded ends of the cells giving them a tadpole-like appearance, and eosinophilic cytoplasm.

Case No. 2. P. J. A. A two-year-old white boy was admitted on 12/4/55 with a two-week history of a hard non-tender diffuse, warm erythematous mass over the left zygoma. There was no history of trauma or pyrexia. Cervical nodes were normal. An incision was made over the apex of the swelling to reveal paper-thin bone. Perforation of the bone with a knife blade permitted the immediate delivery of innumerable grape-like lesions of sarcoma botryoides. Histologic sections showed round and spindle cells with elongated nuclei and bipolar cytoplasm, and a tentative diagnosis of embryonal type rhabdomyosarcoma was made.

The solid tumor consisted of a soft gray mucoid mass filling an enlarged maxillary sinus. The contents of the sinus were curetted. Several days later radical resection of the surrounding tissues was performed and the infraorbital plate, anterior antral wall, and adjacent portion of the nasal walls were removed. The region of the ethmoid part of the remaining left nasal bone including nasal turbinals and cavity were thoroughly curetted. The wound was packed and the gauze was removed progressively from the left nostril. No chemotherapy or radiation therapy was employed.

This child has remained in good health with no recurrence for more than seven years. At a subsequent tonsillectomy no tumor could be felt. The cosmetic appearance is quite acceptable (Fig. 1).

Case No. 3. J. S. A 2½-year-old white boy was admitted on 9/14/60 with the history of a non-tender soft marble-sized round mass, lateral to the lateral canthus of the right eye, first noticed six weeks prior to admission. There was no history of fever or trauma, but the mass was progressively enlarging. There was no cervical lymphadenopathy. Roentgenologic examination showed destruction of right zygoma and the inferior and lateral walls of the right orbit.

Under anesthesia before the excision was begun, a polyethylene catheter was inserted by open technic into the right external carotid artery and 15 micrograms/Kg. of Actinomycin D was administered during the first 15 minutes of surgery. The tumor was found to involve the right zygomatic arch, roof, lateral wall and floor of the orbit, base of the skull behind the pterygoid fossa, and upper lateral portion of the right maxilla. Frozen section was diagnostic of rhabdomyosarcoma. Radical excision of the tumor was carried out which included removal of the lateral roof of the orbit exposing the dura, part of the floor and lateral wall of the orbit. En bloc resection extended laterally from the right subtemporal region to the lateral part of the frontal bone including the zygomatic arch. It was our impression that the tumor had not been completely removed.

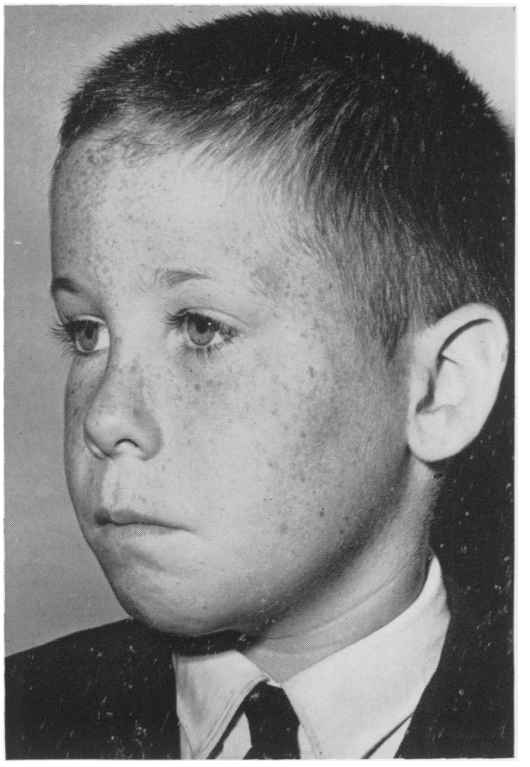

FIG. 1. Facial contour normal and scar beneath left eye and lateral to nose barely visible 7½ years after extensive resection of zygoma and floor of orbit.

Histopathological examination established the diagnosis of rhabdomyosarcoma probably of embryonal type. Round cells and some undifferentiated pleomorphic cells were seen. The cytoplasm was scanty and nuclei were prominent. Cross striations were also noticed. There was partial upper facial paralysis following surgery.

The arterial catheter was left in place and Actinomycin D (15 micrograms/Kg.) was given daily for five days.

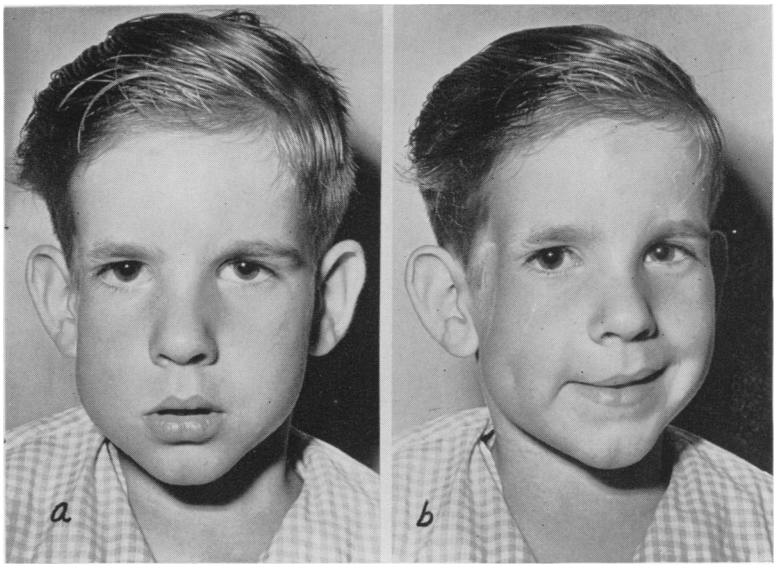

FIG. 2a. Assymetry of facial contour after radical resection of rhabdomyosarcoma. b. On smiling facial nerve damage is evident but passable.

Over 2½ years later no recurrence has been seen. The facial palsy has improved considerably and the cosmetic result is satisfactory (Fig. 2a, b). No further chemotherapy has been given.

Case No. 4. E. K. A 13-year-old white girl was admitted on 6/25/61 with a history of progressive swelling and intermittent pain in left lower jaw of two months' duration. Initially pain was felt and gradually swelling became evident. During this period the patient was treated elsewhere with penicillin, radiation treatment aimed at infection (dose unknown), and two attempts to aspirate the swelling were made. An incision and drainage were finally done and when no purulent material was found, the child was sent to us.

Physical examination revealed a slightly febrile (37.7° C.) child with a $5 \times 5 \times 4$ cm. soft tissue mass which was fluctuant, warm and tender in some areas, adherent to the soft tissues of the left cheek in the right preauricular region. Cervical nodes were slightly enlarged in the upper one-third of the neck in the suprahyoid region. Roentgenographic studies revealed erosion of the lateral and superior margins of the left zygomatic arch.

Antibiotics were administered to the patient for three days and then a biopsy was performed which was diagnostic of rhabdomyosarcoma.

On 6/30/61 radical excision of the tumor was performed. No evident osseous involvement of orbital floor, or cranial cavity, or pterygoid fossa was present. Left parotid, left zygomatic arch, and attached facial muscles were resected en block. Left facial nerve had to be partially resected with the tumor. As surgery was begun, the patient received 4.5 mg. of Vincoleucoblastin through a polyethylene catheter in the left external carotid artery.

Histopathological section showed bizarre multinucleated cells, some of which were arranged around rounded or ovoid spaces. However, a large number of cells were scattered haphazardly. There were scattered round cells and many tadpole cells with acidophilic cytoplasm. This was diagnosed as rhabdomyosarcoma of mixed variety more suggestive of the alveolar type than any other. There was some drainage from the initial site of incision and drainage for a few weeks which spontaneously subsided. The cervical adenopathy rapidly disappeared. She received Vincoleucoblastin 0.1 mg./Kg. intravenously twice a week for two weeks then 0.15 mg./Kg. once a week for one year followed by 1.5 mg./Kg. once every two weeks for the next month and finally she is now receiving 8.5 mg. of Vincoleucoblastin every third week.

There is no evidence of recurrence. Roentgenograms taken in December 1961 and May 1962 show no evidence of osseous lesion. She has tolerated the chemotherapy very well. Plastic procedures to correct her sagging cheek are planned in several months (Fig. 3a, b).

Case No. 5. L. L. A six-year-old boy was admitted on 9/17/61 with a history of proptosis of the left eye of three weeks' duration. This was not accompanied by headache or visual disturb-

ances. Seven days prior to admission he was placed on cortisone which he continued to take until the time of admission.

Physical examination revealed moderate left proptosis with considerable resistance to backward displacement of the left globe. Fundi and sclerae were normal and there was absence of chemosis. Occular tension was within normal range; however, there was slight limitation of levovision. There was some enlargement of supraclavicular nodes. The pharynx was injected. Neurological examination was negative.

Roentgenograph of the skull showed clouding of the left anterior ethmoidal cells. Cerebral angiography established absence of intracranial mass lesion. Intravenous pyelography showed no neuroblastoma. A primary tumor of the retro-orbital area was suspected.

Biopsy of the tumor was performed with a lateral approach to the retro-orbital area. Our microscopic study showed rhabdomyosarcoma.

Two days later exenteration of the left eye was done; both lids were removed. It was felt that the tumor had invaded the ethmoid sinus which was thoroughly curetted. Histopathological section showed tumor to be composed of spindle cells and round cells. Nuclei were hyperchromatic and large. Connective tissue stroma was loose. There was infiltration of skeletal muscles and orbital fat. The boy tolerated the procedure well and four days postoperatively radiation therapy to the operative area was begun and continued with a total dose of 1,200 R. Chemotherapy was begun with 1 mg. of Mitomycin C intravenously once a day for five days, then once every second day for 14 days. He developed severe gastrointestinal toxic reaction, hence chemotherapy was stopped.

He continued to do well and three months postoperatively he was given a course of Mitomycin C, 1 mg. every week for 18 weeks. He has remained symptom free until the present. In April 1963 a tiny nodule on the roof of the orbit proved on biopsy to be rhabdomyosarcoma identical with the original lesion. Roentgenogram showed extensive bony destruction around the orbit and along the sphenoid ridge. A second course of radio-therapy is underway. The boy remains asymptomatic.

Case No. 6. J. S. A seven-year-old white boy was admitted on 7/13/61 with the history of intermittent left otalgia and progressive swelling of the left side of the face for two months. Two weeks prior to admission he developed severe toothache and was treated by a dentist who prescribed antibiotics. This reduced the intensity of pain; however, chewing continued to be painful.

On examination a hard 2×3 cm. mass was found to be fixed to the lateral surface of the ascending ramus of the left mandible. There was marked edema extending from the left temporal fossa to the left nasolabial fold medially. The left upper jugular and digastric lymph nodes were enlarged. Facial roentgenogram and a sialogram drew attention to an area of destruction of the neck of the left mandible and encroachment upon the pharynx by soft tissue tumor of the left

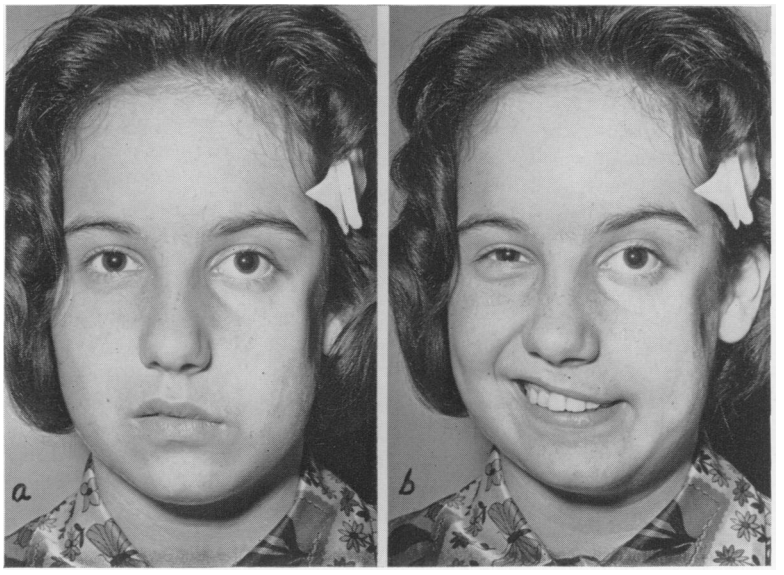

FIG. 3a. Facial asymetry 2 years after removal of rhabdomyosarcoma from pterygoid fossa and adjacent structures. 3b. Face lifting and fascial sling procedure planned to correct facial nerve damage.

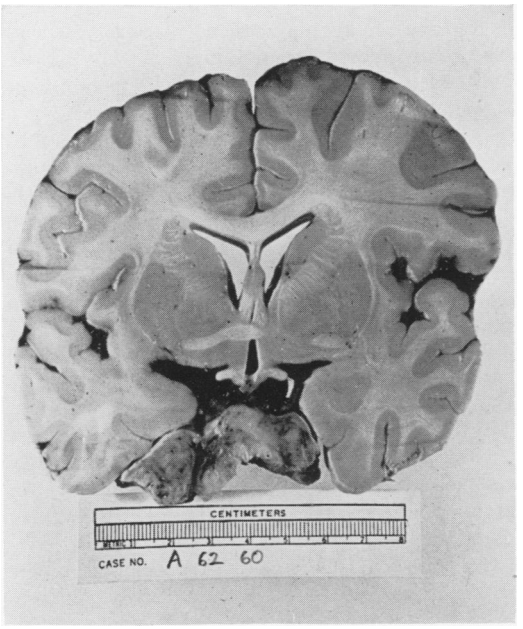

FIG. 4. Infiltration of base of brain after invasion of anterior cranial fossa by rhabdomyosarcoma.

parotid region. The parotid was normally visualized by sialography. Bone marrow did not show any tumor cell.

On 7/14/6 biopsy of the tumor was performed to establish the diagnosis of rhabdomyosarcoma. Two days later definitive radical operation was attempted. Tumor was extending deep in the pterygoid fossa and deep into the skull over the hard palate. Excision was not possible.

Histopathological examination demonstrated skeletal muscle giving rise to tumor cells. Some areas showed pleomorphic tumor cells with large vesiculated nuclei, prominent nucleoli, occasional mitosis. The stroma was scanty and the cell arrangement was nondescript. This is an undifferentiated sarcoma suggestive of rhabdomyosarcoma. The patient received 3.5 mg. of Vincoleucoblastin intra-arterially through the left external carotid artery during surgery. He developed left facial palsy and massive hematoma and edema of the left side of the face which gradually diminished over a period of three weeks. His general condition improved for a few weeks but later he became refractory to all therapy. He received Vincoleucoblastin 3.5 mg. per week for 11 weeks without improvement. This was followed by Mitomycin C 1 to 1.5 mg. for 15 doses, Cytoxan 2 mg. once a day for one and a half months and finally Leurocristine 7.5 mg. per day for two more months. Radiation therapy was given effectively to control pain. One 5/6/62 he was re-admitted in a state of coma and inanition from which he recovered but eventually he expired on 5/31/62.

The tumor had completely occupied the left side of his face. There was marked proptosis of the left eye. The tumor mass extended to the neck inferiorly and superiorly and destroyed the base of the skull and had grown into the anterior cranial fossa. The pituitary could not be identified. There was invasion of the pachymeninges and the pons (Fig. 4). Left submaxillary, sublingual, and parotid glands were invaded by the tumor and there were multiple pulmonary metastases.

Histopathological sections showed tumor to be composed of pleomorphic cells some of which had copious, acidophilic cytoplasm and were polygonal; while others consisted of hyperchromic nuclei and ill defined cytoplasm. Stroma was scanty and cell arrangement was non-descript.

Case No. 7. M. O. A 22-month-old white girl was admitted on 7/20/61 with a history of a marble-sized non-tender mass in the right side of the nose for six weeks prior to admission. She had been afebrile and had received antibiotics for two weeks. A 4×2 cm. hard tumor mass was noted lying obliquely from the upper border of the upper lip to the midpoint of the right side of the nose and projecting into the right nasal cavity completely obliterating it. The skin over the tumor was erythematous. Cervical lymph nodes were not enlarged. Roentgenogram of skull did not show any osseous involvement or encroachment on the paranasal sinuses.

On 7/21/62 biopsy of the tumor was performed which was diagnostic of rhabdomyosarcoma. Two days later radical resection of the tumor was done. A very thin flap of skin was elevated and tumor along with right nasal bone, periosteum of maxilla and a portion of the anterior wall of the maxillary sinus was removed. Some tumor was deep in the orbit and could not be removed. During surgery the patient received 1 mg. of Vincoleucoblastin intra-arterially through the right external carotid artery.

Histopathological studies showed tumor consisting of bizarre cells with large vesicular hyperchromic nuclei, fairly frequent abnormal mitosis. There were scattered round cells occasionally around ovoid spaces. Cross striations were evident suggestive of the alveolar variety of rhabdomyosarcoma. There was osseous invasion. The child was given intravenous Vincoleucoblastin 1 mg. every week for five weeks, then 4 mg. every week for 13 weeks. There was no clinical improvement so Mitomycin C 0.6 mg. per day for

TABLE 1

Name	Sex Age	Site of Origin	Histology	PreOp X-Ray	Surgery	X-ray Rx	Chemo Rx	Result
D. S.	M 2½	Middle ear	Embryonal	Eventual bone destruction mastoid	Biopsy	3,100 R	None	Dead
P. J.	M 2	Maxillary sinus	Embryonal (Botryoides)		Radical excision	None	None	Alive 7 yrs.*
J. S.	M 7	Parotid	Pleomorph	Mandibular destruction	Radical surgery incomplete	for pain only	Vincoleucoblastin intra-arterially during op Vincoleucoblastin Mitomycin Cytoxan Leurocristine	Dead
E. K.	F 13	?Parotid ?Zygoma	Alveolar	Destruction of left zygoma	Incomplete	None	Vincoleucoblastin intra-arterially during op Vincoleucoblastin weekly to present	Alive 2 yrs.*
L. L.	M 6	Muscles of orbit	Embryonal	Clouding of ethmoid	Exenteration of orbit Excision both lids	1,200 R immediately 1,200 R for recurrence	Mitomycin C weekly for 18 weeks then every other day for 14 days	Alive but with tumor asymptomatic*
J. S.	M 2½	Ptergoid muscle	Embryonal	Destruction of right zygoma	Incomplete	None	Actinomycin intra-arterially during op and for 5 days postop	Alive 2½ yrs.*
M. O.	F 1⅝	Upper lip Nasal cavity	Alveolar	No bony destruction	Radical surgery incomplete, two subsequent excision of cervical nodes	None	Vincoleucoblastin intra-arterially during op and weekly for 14 mo.	Dead

* Patients alive and well May 1964.

five days gradually increasing to 1 mg. per week was given until 9/20/62.

On 1/8/62 she was re-admitted with three small masses in the right submandibular region of three weeks' duration. These were excised en block and proved to be metastatic rhabdomyosarcoma of the alveolar type. Chest roentgenogram was normal and there was no local recurrence. On 6/25/62 she developed four smaller grape-sized masses in the right submandibular region. The tumor mass was again removed en block and proved to be metastatic alveolar type rhabdomyosarcoma in lymph nodes.

On 8/2/62 a tumor mass was again noticed in the right submandibular region. Chest roentgenogram showed metastatic lesions in the right lung. Chemotherapy and radiation were continued but her general condition deteriorated. Proptosis of the right eye and chemosis of the right eye developed. She finally expired on 11/9/62.

Discussion

Of the seven patients reported here four are alive. One of these with an incompletely removed rhabdomyosarcoma of the ocular muscles lived 17 months on intermittent chemotherapy with Mitomycin C before there was any external sign of *recurrence*. At that time there was evidence by roentgenogram of extensive bony involvement of the orbit and adjacent skull bones. From our own experience with rhabdomyosarcoma and that reported by others, the Mitomycin C seems to have a repressive action on the growth of the tumor. Even at this writing, 17 months after enucleation, the child is happy and asymptomatic in spite of his metastases.

Of the remaining three patients two had embryonal type rhabdomyosarcoma and one had the alveolar variety. Of these the one embryonal variety presenting in the maxillary sinus had a radical resection aimed at complete extirpation and thought to be successful. The other two with tumors of indeterminate origin around the pterygoid fossa had preoperative intra-arterial infusion of a chemotherapeutic agent into the external carotid artery followed by radical surgery thought to be complete in neither patient. Postoperatively both children were continued on their drugs. Postoperatively 24 and 30 months, respectively, they showed no sign of local or distant recurrence.

Except where elements of the facial nerve were deliberately sacrificed, there is little to show for the radical removal of bone and soft tissue. The ability of pre-adolescents to reconstitute support of facial structure is remarkable. With properly placed skin incisions carefully approximated, very acceptable cosmetic results can be obtained and should encourage surgeons to make the effort to excise these neoplasms completely.

Radiation therapy was given to only one patient prophylactically immediately after the tumor was removed, the patient with the extensive tumor of extra-ocular muscles. Radiation was used in other patients only for the relief of pain and in the treatment of extension of the tumor secondarily.

Five of the seven children received an anti-cancer chemotherapeutic agent. One of those who did not is alive and well seven years postoperatively while the other died within nine months. Of the five who received chemotherapeutic agents, one had Mitomycin C as the primary postoperative drug. Alive seventeen months after operation, the youngster has no metastases.

Three patients received Vincoleucoblastin and of these one is alive 24 months with no evidence of disease while the other two with very similar tumors anatomically both died. One of these was on weekly doses of the drug for 14 months before dying and the other in addition to x-ray therapy for the control of pain also received courses of Mitomycin C, Cytoxan, and Leurocristine without beneficial effect on the tumor.

One patient who received a single course of Actinomycin D administered intra-arterially through the external carotid daily for five days postoperatively is alive and well 30 months postoperatively.

The two patients living and well who received chemotherapy also had an infusion immediately preoperatively into the external carotid artery. Whether or not this was effective alone or had an added effect with the subsequent doses of the same drug postoperatively is a matter of speculation. However, it seems to us significant that both these children are alive in spite of tumor having been left behind at the time of operation. Two other patients received intra-arterial infusion at the start of surgery and have succumbed to their tumors.

During the years covered by our experience with these seven cases, 11 other rhabdomyosarcomas in sites other than the head and neck were treated in this hospital. Ten of these are dead and the eleventh has extensive metastases and is dying. Imminent death was evident in all no later than the 13th postoperative month.

Whether our experience with these seven patients is fortuitous remains to be seen. However, on the basis of what is known about rhabdomyosarcomas of the head and neck in this age group the combination of aggressive surgery, intra-arterial infusion of an anti-cancer drug during the procedure and postoperative anti-cancer chemotherapy seem worthy of continued trial in the present state of our knowledge.

Conclusion

Seven patients with rhabdomyosarcoma of the head in childhood are presented. Three of these are alive and well 24 months to seven years postoperatively. One of them had what was thought to be a complete excision at the time of operation and received no adjunct to surgical therapy. The other two had known incomplete radical resections and had as added therapy intra-arterial infusion at the time of surgery as well as postoperative anti-cancer chemotherapy. The drug used was Actinomycin D in one case, and Mitomycin C in the other. (All patients have survived an additional 11 months.)

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