Primary cerebral rhabdomyosarcoma and the problem of medulloblastoma

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SUMMARY A case of primary rhabdomyosarcoma in the right cerebral hemisphere of a 45 year old woman is reported. This was treated by surgical excision but death occurred 10 months after the first symptom. The histogenesis of such a tumour is discussed. The clinical and pathological features of 15 previously reported similar tumours of the CNS are compared. Most of these occurred in the cerebellum in children where they have been regarded as medulloblastomas (a variant of medulloblastoma), teratomas, or rhabdomyosarcomas. Few have been recorded in adults and only one previously in the cerebrum. All of these tumours tend to have a short clinical course, although survival time seems to be significantly improved by surgical excision followed by radiotherapy. The remarkable morphological similarities between the tumours are discussed. Argyrophilic fibrils were demonstrated in the present case and in an unrelated rhabdomyosarcoma of the jaw. This observation may invalidate the main criterion used for separating medulloblastomas and teratomas from rhabdomyosarcomas in this group of tumours. It is concluded that at present all these tumours should be regarded as rhabdomyosarcomas.

Tumours of the central nervous system (CNS) containing striated muscle elements are rare, especially when teratomas are excluded. A case of primary rhabdomyosarcoma of the cerebrum is reported here. A comparison with other similar tumours which have occurred in the CNS leads to a reappraisal of the concept of medulloblastoma.

CASE REPORT

In July 1969, E.P., a 45 year old housewife (LH No. 504560) developed transitory involuntary jerking movements of the left foot. Three weeks later similar attacks occurred on successive days lasting 5 to 10 minutes on each occasion. The left shoulder was also affected and examination after the attacks showed moderate residual weakness of the left arm and leg. She became drowsy and developed a dense left hemiplegia with some loss of joint position sense on the left, bilateral ptosis, and impairment of conjugate deviation of the eyes to the left. An electroencephalogram indicated a space occupying lesion in the right cerebral hemisphere, and a carotid angiogram showed an avascular lesion in the right parietal zone with 1.5 cm shift of the midline vessels to the left and evidence of early tentorial herniation.

At craniotomy a small intracerebral haematoma was discovered in the right posterior frontal region, and this was evacuated. Biopsy of the wall of the cavity showed only gliosis. Her level of consciousness, but not the hemiplegia, improved at first, but over the next two weeks deteriorated to the previous level. Re-exploration showed a cerebral abscess at the site of the previous haematoma but this was sterile on culture. After this there was a further temporary improvement but a few days later she was again deeply unconscious and had a left homonymous hemianopia. At the beginning of September the craniotomy was reopened and the cavity decompressed but there were no new findings and her condition did not improve. Three weeks later a multilocular abscess in the right cerebral hemisphere was excised *in toto*. Histological examination showed areas of undifferentiated malignant tumour of uncertain origin in the wall of the abscess. Over the next five months there was a gradual improvement in her condition and she was able to walk with the aid of a tripod. The left arm remained weak and the visual field defect was unchanged. During March 1970 she became drowsy and complained of headache. There was a precipitous deterioration in her level of consciousness, with raised intracranial pressure and bilateral pyramidal signs. One hundred and fifty

millilitres of opalescent fluid were aspirated from the craniotomy site but she became deeply unconscious and remained so until she died towards the end of April 1970, 10 months after the onset of her illness.

PATHOLOGY

SURGICAL MATERIAL (SD/6558/69) The material received after total excision of the abscess consisted

bone. The brain (1,107 g) was soft with flattening of the cerebral convolutions on the left and bilateral uncal grooving. Mottled haemorrhagic tumour was visible through a 5.0 cm diameter defect in the right parietal cortex and in this region the left hemisphere bulged across the midline. The brain was fixed in 4% formol-saline for three weeks and then sliced. The slices showed a large tumour, up to 5.5 cm in

FIG. 1. *Surgical material showing a pleomorphic cellular tumour with occasional mitoses. Capillary blood vessels are seen within the tumour. Haematoxylin and eosin, $\times 350$.*

of a ragged roughly spherical mass of soft brain tissue 7.0 cm in diameter, weighing 176 g. It contained multilocular abscess cavities up to 4.5 cm in diameter. Parts of the wall were thick and fibrous but other areas adjoined brain tissue without fibrous demarcation. Microscopy showed large areas of necrosis and granulation tissue with surrounding gliosis but areas of undifferentiated pleomorphic tumour of uncertain origin were also present (Fig. 1). Review of these sections after the necropsy material was available revealed some strap-like cells with cross-striations within the areas of granulation tissue.

NECROPSY (No. 85/70) Necropsy was performed 40 hours after death. The body weighed 30.4 kg and was 162 cm long. There was a large surgical scar in the scalp of the right frontoparietal region deep to which there was an oval defect in the calvarium, 9.5 $\times$ 8.5 cm. The right cerebral cortex was adherent to the scalp in this area and was dissected free with difficulty. A plastic reservoir drained the left lateral ventricle through a small trephine in the left parietal

maximum diameter, which occupied and distorted the middle third of the right cerebral hemisphere (Fig. 2). It extended from the level of the optic chiasm to the posterior parietal region where it occupied the body of the lateral ventricle. Superolaterally it bulged through the cortical defect where it was partly covered by fresh blood clot, and partly by gliotic capsule. The cut surface showed some firm white areas and other multilocular cystic areas which contained green/grey gelatinous material (Fig. 2). There was considerable disorganization of the ventricular system by the tumour on the right side and some dilatation on the left. Both frontal lobes were oedematous. The brain-stem, cerebellum, spinal cord, and cerebral vessels were normal.

There was a well-developed bilateral bronchopneumonia in the lower lobes of both lungs. The remaining organs were normal and there was no evidence of tumour elsewhere.

MICROSCOPY The gelatinous and cystic areas of the tumour (Fig. 2) were composed of amorphous eosinophilic and necrotic material with some areas

FIG. 2. Right cerebral tumour at necropsy. It distorts the ventricular system below and is partly covered by gliotic capsule and blood clot above where it penetrates the cortical surface. The cut surface shows pale solid areas and darker cystic areas.

FIG. 3. Necropsy material showing strap-like spindle cells of varying size and a large ovoid-cell with abundant granular cytoplasm. H and E, $\times 350$.

FIG. 4. Cross-striations in a strap-cell at necropsy. Phosphotungstic acid haematoxylin, $\times 1400$.

FIG. 5. Small cell areas which resemble those seen in the surgical material. Transitional spindle cell forms are present. H and E, $\times 350$

of granulation tissue. A malignant tumour of variable histological pattern was present in the firm white areas (Fig. 2) and in other areas bordering on adjacent brain tissue. In some places it had widely dispersed stellate cells with few mitoses within a loose connective tissue stroma; the appearances resembled embryonic mesenchyme. In other areas there were interlacing bundles of spindle cells, many of which were strap-like with granular eosinophilic cytoplasm (Fig. 3). Some giant, oval, or round cells with similar abundant cytoplasm were also present

(Fig. 3). Cross-striations were occasionally seen in the strap forms on haematoxylin and eosin sections and were numerous in sections stained with phosphotungstic acid haematoxylin (Fig. 4). Areas of undifferentiated cells which resembled those seen in the surgical material were present particularly at the growing edge (Fig. 5). They contained clusters of small cells with a moderate number of mitoses mixed with larger cells which showed occasional giant and multinucleate forms. Early transitions to spindle cell forms were clearly seen (Fig. 5) and thin-

FIG. 6. Frozen section of necropsy material from the present case. Argyrophilic fibrils radiate from cells of all kinds. Weil-Davenport, $\times 560$.

FIG. 7. Frozen section of necropsy material from an unrelated rhabdomyosarcoma of the jaw. There are occasional short argyrophilic fibrils arising from tumour cells. Weil-Davenport, $\times 560$.

walled vascular channels were present in the loose connective tissue background. Nervous tissue was not present within the tumour substance and no other ectodermal or endodermal derivatives were seen.

Frozen sections of formalin fixed tumour tissue, taken to include all the areas mentioned, were stained by the silver techniques of Weil-Davenport, Bielschowsky, and Scharenberg. Control sections were performed on normal brain tissue. By each method numerous argyrophilic fibrils of varying size were demonstrated radiating from cells of all kinds (Fig. 6). In view of this apparently non-specific argyrophilia, tissue from an undifferentiated embryonal rhabdomyosarcoma of the jaw in a 22 year old man was stained in a similar fashion. Again a few argyrophilic fibrils were seen despite the anaplastic nature of the tumour (Fig. 7). Electron microscopy was attempted on the tumour tissue but the electronmicrographs were of poor quality due to the inappropriate fixation in formol-saline. However, fragmented and disorganized myofibrils composed of filaments with the appearance of actin and myosin were seen in the cytoplasm of both the strap-like cells and the small undifferentiated cells.

Sections from the lung confirmed the presence of moderate bilateral bronchopneumonia. No significant abnormality was seen in the other tissues of the body and there was no evidence of tumour deposits elsewhere.

DISCUSSION

The necropsy confirmed the presence of a primary tumour of the right cerebral hemisphere with no tumour deposits elsewhere. In view of the light and electron microscope appearances a diagnosis of rhabdomyosarcoma seemed most likely and the absence of derivatives from other embryonic germ layers helped confirm this. In the biopsy material the diagnosis was obscured by a severe inflammatory reaction and predominance of the undifferentiated component of the tumour. The symptoms and signs corresponded with the site of the tumour at necropsy but the clinical course was unusual. The initial event was probably haemorrhage within the tumour from thin-walled vascular channels, and an abscess formed after the blood clot was evacuated.

Rhabdomyosarcomas are rare tumours outside of the central nervous system and fall into two distinct but related groups (Evans, 1966; Stout and Lattes, 1967). In adults they occur

mainly in the soft tissues of the trunk and extremities; they are often pleomorphic with little evidence of cross-striated cells, although more differentiated forms have been recorded (Evans, 1966). In children and adolescents the head and neck and urogenital tract are the main sites of origin. In these tumours more differentiation may occur and cells with cross-striations are more frequently seen. The fact that many rhabdomyosarcomas arise in tissues that do not normally contain striated muscle has led some authorities to believe that these tumours derive directly from unstable mesenchyme which undergoes neoplastic change (Evans, 1966; Willis, 1967). A similar origin from mesenchyme would also adequately explain the presence of such a tumour in the central nervous system. The alternative is that the present tumour is related to the mixed mesenchymal and neuro-epithelial tumours which have recently been described (Goldman, 1969; Shuangshoti and Netsky, 1971). These tumours differ from the present case in that they contain a combined glioma and sarcoma in which varying degrees of differentiation into fibroblastic, chondroblastic and rhabdomyoblastic elements have occurred. They are probably related to gliosarcomas (Rubinstein, 1956). An overgrowth of a rhabdomyoblastic element in such a tumour could mimic a rhabdomyosarcoma. However, derivation from unstable mesenchyme would seem a more likely explanation.

Only one previous case of a cerebral rhabdomyosarcoma has been found (Koide, 1957) and this is poorly documented. There are, however, 15 reports of primary tumours of the CNS which might also be regarded as rhabdomyosarcomas. The clinical and pathological details of these are summarized in the Table together with the present case.

The first 11 listed are similar to each other (Table). They are all cerebellar tumours which have occurred in children aged 2 to 11 years and all are known to have been in the midline. The sex ratio is 4F:7M. The clinical histories are of variable length (two weeks to nine months). In many cases death occurred before or soon after surgery but in three cases (3, 4, and 8) surgical excision followed by radiotherapy gave a significant improvement in survival time (12 to 23 months). Distant metastases have not occurred

TABLE

DETAILS OF POSSIBLE RHABDOMYOSARCOMAS OF CNS

No.	Source	Sex	Age (yr)	Diagnosis	Site	Microscopic features	Other necropsy findings	Length of history (months)	Treatment	Survival time (months)
1	Marinesco and Goldstein (1933)	F	5	MM	Vermis	Small cell areas; cross-striated cells near vessels	No tumour elsewhere	3	None	3
2	Russell and Rubinstein (1971) (case from 1934)	M	2½	MM	Vermis	Small cell areas; cross-striated spindle cells	Brain only examined	—	Decompression	4/28
3	Zülch (1942)	M	5	MM	Vermis	Medulloblast-like cells; smooth muscle-like cells near vessels	No necropsy	3	Excision. DXT	12
4	Ingraham and Bailey (1946) (case 4)	M	10½	T	Midline cerebellum	Small cells with neurofibrils; large cells with cross-striations	No necropsy	—	Excision. DXT	12
5	Bofin and Ebels (1963)	M	6	MM	Vermis and right cerebellum	Cellular areas resembling medulloblasts; cross-striated spindle cells	No tumour elsewhere	8	Partial excision	v. short
6	Boellaard (1964)	M	8	MM	Vermis	Cellular areas resembling neuroblasts; cross-striated spindle cells	Leptomeninges infiltrated. Brain only examined	Short	None	v. short
7	Gullotta (1967) (case 11)	F	3½	MM	Vermis	Small cell areas; cross-striated spindle cells	No general necropsy	9	Exploration	v. short
8	Legier and Wells (1967)	M	3½	RS	Vermis	Stellate mesenchyme; spindle cells with cross-striations. No neuroblastic forms	Extensive leptomeningeal spread in cord	Short	Excision. DXT	23
9	Shuangshoti <i>et al.</i> (1968)	F	4	RS	Vermis	Small cells, pleomorphic cells, spindle cells with cross-striations. No neuroblastic forms	Leptomeninges of brain base infiltrated	2/52	None	13/28
10	Unpublished case of R. S. Beckett quoted in 9	F	9	RS	Midline cerebellum	Similar to case 9	—	—	—	—
11	Misugi and Liss (1970)	M	7½	T	Midline cerebellum	Small cell areas with neuroblastic forms; cross-striated spindle cells	No necropsy	Short	Decompression	3/28
12	O'Connell (1946) (case 1)	F	5	T	Lumbar cord	Spindle cells with cross-striations	Spread in spinal cord associated with spina bifida	6	Exploration	1
13	Lopes de Faria (1957)	F	52	RS	Left cerebellar hemisphere	Stellate mesenchyme; spindle cells with cross-striations. No neuroblastic forms	No tumour elsewhere	5	None	v. short
14	Koide (1957)	M	15	RS	Right cerebral hemisphere	Pleomorphic cells; small cells, cross-striated spindle cells. No neuroblastic forms	No tumour elsewhere	4	Decompression DXT	2
15	Galatioto and Gaddoni (1971) (case 1)	F	26	MY	Left cerebellar hemisphere	Small cell areas; spindle-cell areas. No striations seen	No general necropsy	Short	Exploration	v. short
16	Present case	F	45	RS	Right cerebral hemisphere	Cellular pleomorphic areas; bundles of cells with cross-striations; stellate mesenchyme	No tumour elsewhere	6/52	Excision	10

MM = medullomyoblastoma; T = teratoma; RS = rhabdomyosarcoma; MY = myosarcoma. DXT = radiotherapy.

but cases 6, 8, and 9 showed infiltration of the leptomeninges. The microscopic appearances of individual tumours are strikingly similar with descriptions of cellular small cell areas, and less cellular spindle cell areas mentioned in many reports. Spindle cells with cross-striations are described in every case except that of Zülch (1941) who did not demonstrate stripes and regarded these as smooth muscle cells (case 3). However, his case resembles the others in all other respects and must be included in this group of tumours. Misugi and Liss (1970) claimed to have demonstrated axon-like structures in the electronmicrographs of their tumour (case 11) but their illustrations are not convincing and they also described glial fibres which may indicate an admixture of normal neural tissue within their tumour.

Six of the tumours in this group (cases 1, 2, 3, 5, 6, and 7) were called medulloblastomas mainly because neurofibrils were demonstrated within the small cell areas. Other authors (cases 4 and 11) felt that this finding indicated a teratomatous origin. These tumours with apparent neuroblastomatous elements have usually been regarded as variants of medulloblastoma, but recently Russell and Rubinstein (1971) have preferred to call them malignant teratoid tumours. Neural elements were not demonstrated in the remainder (cases 8, 9, and 10). Even so these pure rhabdomyosarcomas have been related to medulloblastomas by most authors, although it has been suggested that they represent rhabdomyoblastic differentiation in an embryonal sarcoma (Russell and Rubinstein, 1971). However, because of the many similarities described above it would seem that the first 11 cases listed (Table) belong to the same group of tumours.

The tumour described by O'Connell (1946) occurred in the lumbar cord in a 5 year old girl and was associated with spina bifida (case 12). This was probably a rhabdomyosarcoma arising in a hamartoma associated with the congenital defect. The remaining tumours (cases 13, 14, 15, and 16, present case) occurred in the cerebrum or cerebellum of adults and had a rapid clinical course. The microscopic appearances are very similar. Galatioto and Gaddoni (1971) failed to demonstrate cross-striations (case 15), but

examination of illustrations and paraffin sections of their case shows close similarities in all other respects. Clearly it would seem reasonable to classify these tumours together and examine their relationship to the childhood group.

Although the adult and childhood tumours occur in different sites, they do not vary in behaviour or morphology. In both groups the clinical course is short and stormy and a comparison of the histological appearances reveals remarkable similarities. Cellular areas composed of small round or oval cells with some pleomorphism are described in both groups as are less cellular areas of spindle cells. Foci of primitive mesenchyme and cells with cross-striations are also a common feature. It has been possible to examine sections from the childhood tumour described by Russell and Rubinstein (1971) at this hospital (case 2) and the cellular areas of that tumour are indistinguishable from similar cellular areas in the present case. In addition there are cells present which are transitional between the spindle and round cell elements in the present case. On morphological grounds therefore, there is a strong case for including both childhood and adult tumours in the same group.

The demonstration of neurofibrils by silver impregnation techniques has been used to distinguish a neuroectodermal element in those tumours of the childhood groups called medulloblastoma or teratoma. Argyrophilic processes have been demonstrated in the present case and also in material from a primary rhabdomyosarcoma of the jaw. The reaction in this type of tumour may therefore be non-specific, a finding which invalidates the main criterion for distinguishing a neuroblastomatous element.

It is concluded, therefore, that on present evidence it would be best to regard all these tumours as rhabdomyosarcomas.

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REFERENCES

- Boellaard, J. W. (1964). Ein Medulloblastom mit quergestreiften Muskelfasern. *Archiv für Psychiatrie und Nervenkrankheiten, vereinigt mit Zeitschrift für die gesamte Neurologie und Psychiatrie*, **206**, 228–236.
- Bofin, P. J., and Ebels, E. (1963). A case of medulloblastoma. *Acta Neuropathologica*, **2**, 309–311.
- Evans, R. W. (1966). *Histological Appearances of Tumours*. 2nd edition, p. 48–57. Livingstone: Edinburgh.
- Goldman, R. L. (1969). Gliomyosarcoma of the cerebrum. *American Journal of Clinical Pathology*, **52**, 741–744.
- Galatioto, S., and Gaddoni, G. (1971). Miosarcomi primitivi del SNC. *Acta Neurologica (Bari)*, **26**, 297–302.
- Gullotta, F. (1967). *Das sogenannte Medulloblastoma*. Springer: Berlin.
- Ingraham, F. D., and Bailey, O. T. (1946). Cystic teratomas and teratoid tumors of the central nervous system in infancy and childhood. *Journal of Neurosurgery*, **3**, 511–532.
- Koide, O. (1957). A case of primary rhabdomyosarcoma of the brain [Japanese]. *Gann*, **48**, 645–647.
- Legier, J. F., and Wells, H. A., Jr. (1967). Primary cerebellar rhabdomyosarcoma. Case report. *Journal of Neurosurgery*, **26**, 436–438.
- Lopes de Faria, J. (1957). Rhabdomyosarcoma of cerebellum. *Archives of Pathology*, **63**, 234–238.
- Marinesco, G., and Goldstein, M. (1933). Sur une forme anatomique, non encore décrite, de médulloblastome; médullo-myoblastome. *Annales d'Anatomie Pathologique*, **10**, 513–525.
- Misugi, K., and Liss, L. (1970). Medulloblastoma with cross-striated muscle. A fine structural study. *Cancer (Philad.)*, **25**, 1279–1285.
- O'Connell, J. E. A. (1946). The subarachnoid dissemination of spinal tumours. *Journal of Neurology, Neurosurgery, and Psychiatry*, **9**, 55–62.
- Rubinstein, L. J. (1956). The development of contiguous sarcomatous and gliomatous tissue in intracranial tumours. *Journal of Pathology and Bacteriology*, **71**, 441–459.
- Russell, D. S., and Rubinstein, L. J. (1971). *Pathology of Tumours of the Nervous System*, 3rd ed., p. 15. Arnold: London.
- Shuangshoti, S., and Netsky, M. G. (1971). Neoplasms of mixed mesenchymal and neuroepithelial origin. *Journal of Neuropathology and Experimental Neurology*, **30**, 290–309.
- Shuangshoti, S., Piyaratn, P., and Viriyapanich, P. L. (1968). Primary rhabdomyosarcoma of cerebellum—necropsy report. *Cancer (Philad.)*, **22**, 367–371.
- Stout, A. P., and Lattes, R. (1967). Tumors of the soft tissues. In *Atlas of Tumor Pathology, 2nd Series, Fascicle 1*, p. 134–144. Armed Forces Institute of Pathology: Washington, D.C.
- Willis, R. A. (1967). *Pathology of Tumours*. 4th edn., p. 757–771. Butterworths, London.
- Zülch, K. J. (1941). Ein Medulloblastom mit glatten Muskelfasern. *Archiv für Psychiatrie und Nervenkrankheiten, vereinigt mit Zeitschrift für die gesamte Neurologie und Psychiatrie*, **114**, 349–352.