MEDULLOBLASTOMA. A REPORT OF 201 CASES WITH EMPHASIS ON THE RELATIONSHIP OF HISTOLOGIC VARIANTS TO SURVIVAL

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Medulloblastoma has invariably been associated with a poor prognosis. However, it has been shown that such tumors in adults have a slightly better prognosis than in children. We have studied 201 such neoplasms and attempted to correlate survival with several factors. In our series, adults survived longer (average 50 months) than children (average 11 months), and females (average 31 months) slightly longer than males (21 months). Location of the primary tumor was also of significance since patients with neoplasms primarily located in a cerebellar hemisphere showed a better survival (47 months) than those located in the cerebellar midline (17 months). The histologic typing of the tumor was also important. Patients with "desmoplastic" medulloblastomas had an average survival of 51 months, while those with the "classical" medulloblastomas had an average of 18 months only. The majority of the desmoplastic neoplasms occurred in adults and in cerebellar hemispheres rather than the midline. Further differentiation within the tumor toward the neuroblastic or the glial lines was evident in 51 neoplasms, and no significant differences in survival were noted among them. Four patients eventually developed extracranial metastases, and two were associated with meningiomas.

SINCE BAILEY AND CUSHING, IN 1925,[8] distinguished the medulloblastoma as a specific entity, a voluminous literature has accumulated on that subject with about 1,500 cases reported[1,8,23,27] and at least one book entirely devoted to it.[11] Many authors studied the different factors affecting the prognosis of this neoplasm. These efforts were mainly concentrated on the methods of therapy[7,10,13,20,24,31,32] and age of onset.[36,40,41] However, no serious attempts were made to correlate survival data with the morphology of medulloblastoma.

In 1964, Rubinstein and Northfield[38] subclassified the medulloblastoma into two main categories, the "classical" and the "desmoplastic" with a transitional form. Also, it has been reported that this neoplasm may differentiate into the glial or the neuroblastic line.[2,9,11,22,39] The purpose of this paper is to examine the effects of age, sex, location of tumor, and particularly histologic variants on the prognosis of medulloblastoma.

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MATERIALS AND METHODS

The source of material was combined from the Cleveland Clinic (Dr. W. James Gardner's surgical collection) and from the Armed Forces Institute of Pathology (the Frazier-Grant tumor collection of 1,628 neoplasms which were transferred to the AFIP from the University of Pennsylvania School of Medicine in 1953 by Dr. Francis C. Grant).

All tumors reported as medulloblastomas, neuroblastomas of cerebellum, primary sarcomas of cerebellum, and atypical gliomas confined to the cerebellum were examined. Two hundred and twenty-three such tumors were reviewed (137 AFIP, 88 CC). Of these, 201 were classified as medulloblastomas (129 AFIP, 72 CC).

All sections were stained with hematoxylin and eosin. Reticulin stain, phosphotungstic acid hematoxylin, and Chen Bodian stains were used when needed.

HISTOLOGIC PICTURE

The slides were studied with the objective or classifying them as "classical medulloblastomas" according to the original description by Bailey and Cushing[3,4] and later emphasized by others,[15,38,39] or as "desmoplastic medullo-

blastomas" as described by Rubinstein and Northfield,[38] and to observe whether there was evidence of further differentiation in them. The description below will not be too detailed due to the excellent descriptions already present in the literature.

"Classical" medulloblastomas: This is a cellular tumor consisting of small round to pear-shaped cells with round-to-oval hyperchromatic nuclei that show a coarse chromatin pattern. The cytoplasm is scant, and cellular borders are not well identified (Fig. 1). Mitoses may be abundant. On low power, these cells form irregular sheets, but occasionally rosettes of the Homer-Wright type are formed[15] (Fig. 2), which are indicative of neuroblastic differentiation.[39] The cells forming these rosettes are carrot shaped with tapering unipolar processes, being bipolar on occasion. Rarely, neurofibrils may be demonstrated in these rosettes with the silver stains. Differentiation toward ganglion cells was evident on two occasions (Fig. 3). Spongioblastic and astrocytic differentiation may be noted (Fig. 4), with glial fibrils stained positively with the PTAH method. Also, oligodenroglia may be found within this tumor.

Blood vessels are inconspicuous, in general;

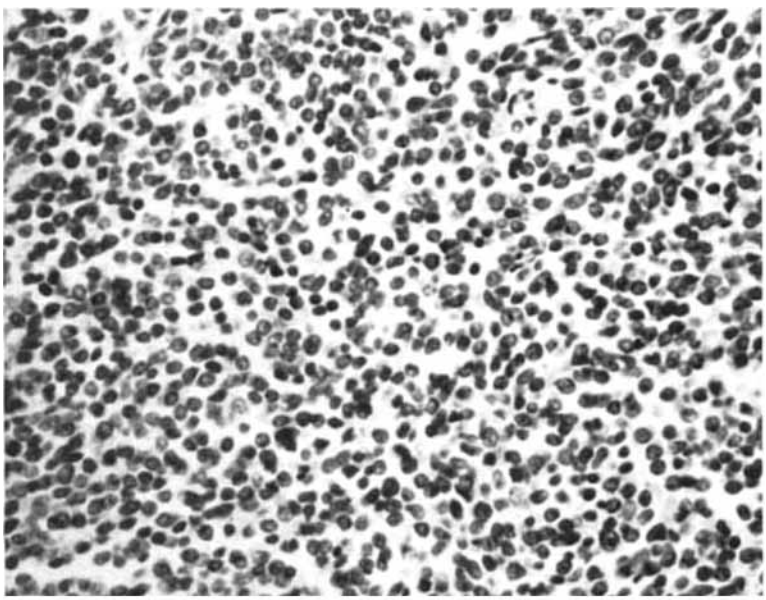

FIG. 1. General appearance of the "classical" medulloblastoma. Round to pear-shaped cells with round to oval hyperchromatic nuclei and poorly identified cytoplasmic borders (H and E, ×400).

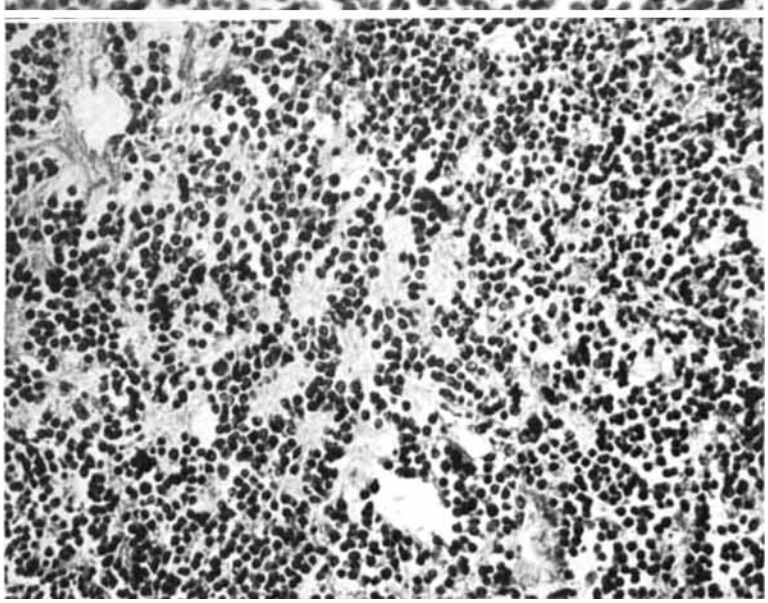

FIG. 2. Homer-Wright rosettes in medulloblastoma (H and E, ×200).

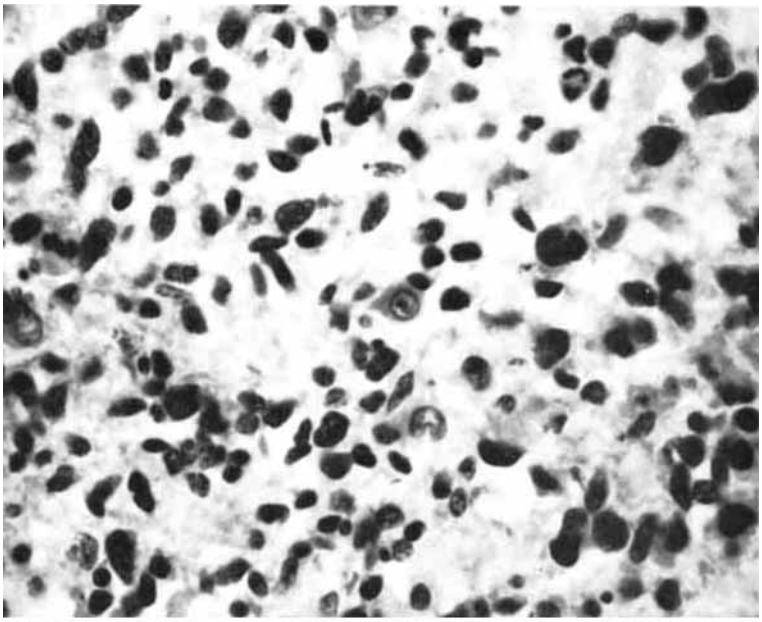

FIG. 3. Ganglion cells are seen in the center surrounded by medulloblastoma cells (H and E, ×500).

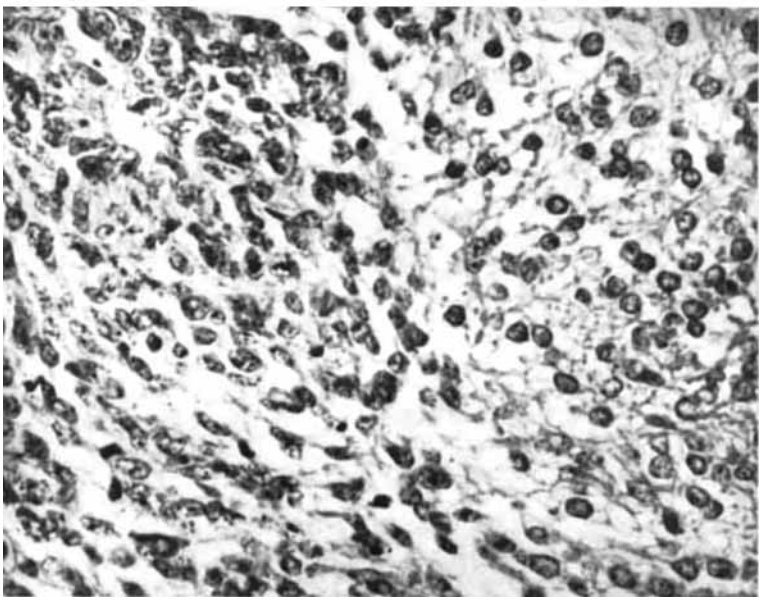

FIG. 4. Astrocytic differentiation in medulloblastoma. Note the fine fibrils (PTAH, ×400).

however, endothelial proliferation may occur and become pronounced. Macrophages were seen in one case filling the lumens of many small capillaries, but their significance is not know.

"Desmoplastic" medulloblastoma: This tumor is made of islands of cells entirely devoid of connective tissue, surrounded by and delineated from the rest of the tumor by an elaborate network of fibrous tissue rich with reticulin (Figs. 5, 6). The cells forming the islands are small, round to oval with dark staining round or oval nucleus. A nucleolus is sometimes identified in the paler staining nuclei. The cytoplasm is scant and polar. A delicate fibrillary background is noted in the islands. The tumor cells in the connective tissue surrounding these islands are essentially identical to those within the islands. However, due to compression factors, there was some distortion and elongation of the cells. The background does not show the fibrillary appearance characteristic of most neuroectodernal tumors and is made up of thick bundles of collagenous tissue with many reticulin fibers and few fibroblasts which are larger than the

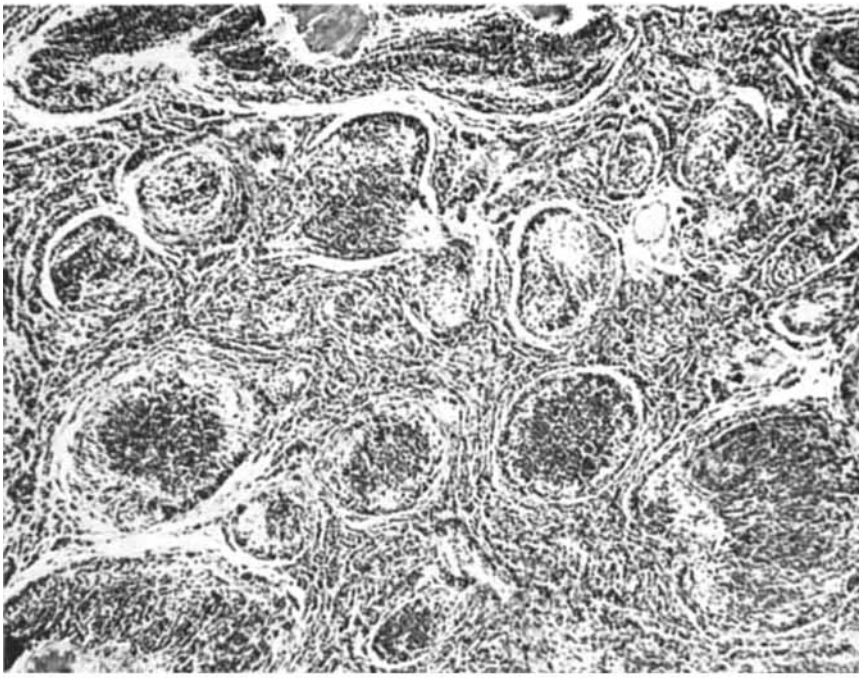

FIG. 5. Glomeruloid pattern of the "desmoplastic" medulloblastoma (H and E, ×80).

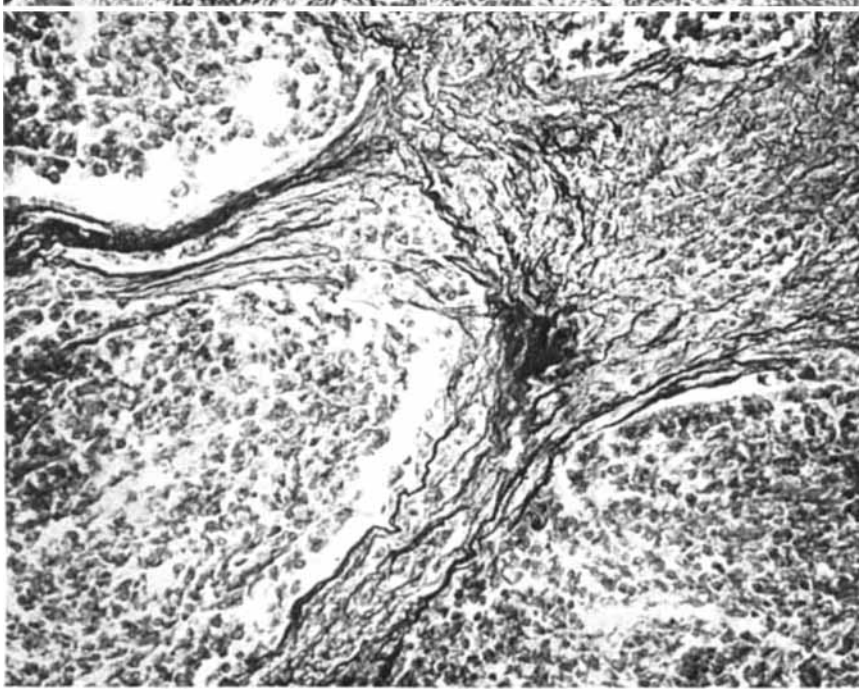

FIG. 6. Reticulin stain to show the elaborate network of reticulin fibers surrounding an island of cells entirely devoid of connective tissue (Reticulin, ×200).

tumor cells, elongated and with an oval vesicular nucleus and a prominent nucleolus.

STATISTICAL DATA

Of the 201 cases accepted as medulloblastomas, 12 were eliminated due to insufficient follow-up data. Five patients died just prior to operation and 71 died within one month after the operation and were considered as postoperative deaths; eight were treated by surgery only. The remaining 105 patients were treated by surgery and radiotherapy, had sufficient pathologic and clinical data, and lived more than one month postoperatively. The survival rates apply to these 105 patients only, unless indicated otherwise.

General prognosis: The average survival

was 25 months for the entire group. Forty-seven patients were alive at the end of one year (a survival rate of 44%), Table 1. Twenty-three (22%) were alive at the end of 3 years, 13 (12%) at the end of 10 years, and seven (6%) lived 10 years or longer. Three of these died 149, 170, and 190 months later, and four were alive 12, 15, 17, and 19 years later.

Age: Of the 105 cases, 67 patients 15 years or under (children) had an average survival of 11 months; 38 were 16 years or over (adults) and lived an average of 50 months. The 1-year survival was 24% for the children and 82% for the adults. The 3-year survival was 7% for the children and 47% for the adults. The 5-year survival was 1% for the former group and 16% for the latter (Table 1). Of the seven patients who survived more than 10 years, one was a child and six were adults.

Sex: There were 76 males and 29 females. The average survival was 21 months for males and 31 months for females. Females over 16 years of age had an average survival of 55 months; those under 16 had an average survival of 12 months. Adult males had an average survival of 44 months, while the male children had an average survival of 10 months. Five of the long-term survivors were males and two were females. Of the entire 201 patients, 147 were males and 54 were females (a ratio of 3:1).

Location of tumor: There were 78 tumors located primarily in the cerebellar midline and 27 primarily in the cerebellar hemisphere. Of the latter 27, 17 were located in the left hemisphere and 10 in the right. The average survival for patients with midline neoplasms was 17 months and for those with hemispheric neoplasms 47 months. It is important to point out that six of the seven long-term survivors had tumors located primarily in the cerebellar hemisphere. Of the total 201 neoplasms, 40 were hemispherical in location and 161 were primarily midline tumors.

"Desmoplastic" vs. "classical" medulloblastoma: Of the 201 tumors, 42 were "desmoplastic" and 159 were "classical." No cases were classified as transitional, since it was felt that eliminating this category would make the classification simpler and the study more objective. Of the 105 cases studied for survival, 21 were classified as desmoplastic and 84 as classical. The desmoplastic group had an average survival of 51 months—71 months for the adults and 19 months for the children. The 1-year survival for all patients in this group was 67%—91% for adults and 33% for the children. Three-year survival was 48%—75% for adults and 22% for children. Five-year survival was 33%—50% for adults and 11% for children. Ten-year survival was 24%—41% and 0% for the two groups, respectively (Fig. 7). The classical type had an average survival of 18 months. The 1-year survival for this group was 39%—77% for adults and 22% for children. The 3-year survival was 14%—34% and 5% for the two groups, respectively. The 5-year survival was 7%—15% and 4% for the three previous categories. The 10-year survival was 2%—4% for adults and 2% for children (Table 2, Fig. 7). It should be pointed out that of the seven long-term survivors, five were classified as desmoplastic and two as classical.

DISCUSSION

Prognosis in medulloblastoma has generally been regarded as poor.[12,14,17,35,42] Occasionally, there have been reports of patients with long survival.[24,35] Efforts have been made to study the influence of different factors on prognosis. However, the relationship of the histology of the tumor upon survival did not receive much attention, and the few studies available were inconclusive.[13,40] Rubinstein and Northfield,[38] in 1964, reviewed the subject of cerebellar sarcoma and considered these as a desmoplastic variant of medulloblastoma. We tend to agree with their classification rather than with that of Langheim et al.[25] who described a series of 24 cerebellar tumors and considered them cerebellar sarcomas of mesenchymal origin. This brings us to the subject of histogenesis of medulloblastomas. Much has been written on that subject, and the reader is referred to the litera-

TABLE 1. Survival Data for All 105 Patients Who Lived One Month or Longer Postoperatively, Subclassified According to Age

		1 year	2 years	5 years	10 years
All patients	(105)	47 (44%)	23 (22%)	13 (12%)	7 (6%)
Over 15 years of age	(38)	31 (82%)	18 (47%)	10 (26%)	6 (16%)
15 and under	(67)	16 (24%)	5 (7%)	3 (4%)	1 (1%)

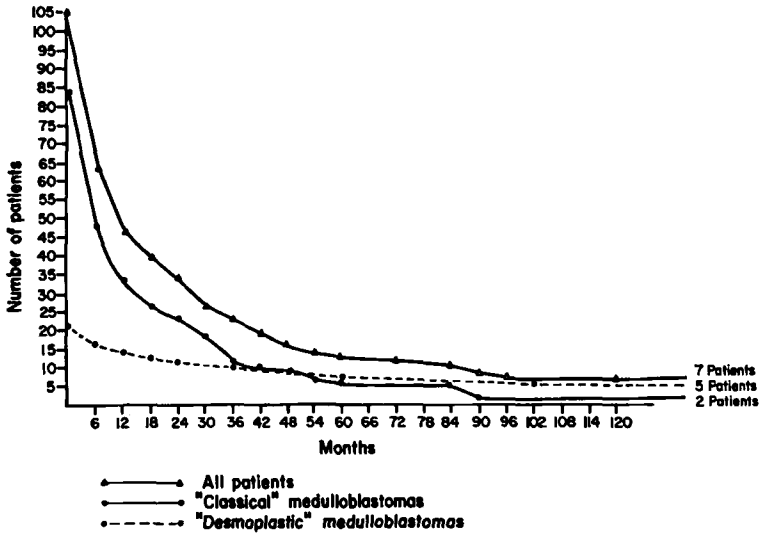

FIG. 7. Survival of 105 patients with medulloblastoma treated by a combination of surgery and irradiation and survival for more than one month postoperatively. There were 21 patients whose tumors were classified as "desmoplastic" and 84 as "classical" medulloblastoma.

ture.[2,4,11,18,19,21,23,25,38] Suffice it here to say that we agree with the neuroectodermal origin of medulloblastoma and with Rubinstein and Northfield's classification. Our series shows that the average survival for the "classical" group was 18 months and for the "desmoplastic" group 51 months. It also shows that among the entire series of 201, there were 42 desmoplastic medulloblastomas; 22 of these were located in a cerebellar hemisphere and of these 22, 17 were in adults. This slightly more favorable prognosis for the desmoplastic group is in agreement with the findings of others.[5,16,23] Significant differences in prognosis were noted between medulloblastoma primarily located in the cerebellar midline and those located in a cerebellar hemisphere. Average survival was 17 months for the midline and 47 months for the hemisphere. This fact was not fully appreciated before, although it may be concluded from the works of Cushing,[12] and Spitz,[41] and Ringertz.[36] Six of the seven long-term survivors had a hemispherical tumor.

Survival was remarkably better for adults (average 50 months) than for children (average 11 months). It was also slightly better for females (average 31 months) than for males (average 21 months). Differentiation within the neoplasm did not seem to play a big role in prognosis. Neuroblastic differentiation evidenced by the formation of rosettes[39] was present in 38 neoplasms. The average survival of these patients was 27 months. There were 67 tumors with no such differentiation, and they had a 24-month average survival.

Astrocytic differentiation was present in eight instances. The average survival was 29 months. Three neoplasms showed cligodendroglial differentiation, and these patients lived 3, 11, and 58 months, respectively. Two neoplasms showed differentiation towards ganglion cells, and these patients lived 17 and 69 months, respectively.

Four patients in this series developed extracranial metastases to the bones, lung, and pleura. All of these underwent surgery before, and all neoplasms were of the "classical" variety. The patients lived 18, 27, 67, 90, and

TABLE 2. Survival Data for All 105 Patients Who Lived One Month or Longer Postoperatively, Subclassified According to Type of Tumor and Age

		1 year	3 years	5 years	10 years
"Desmoplastic"	(21)	14 (67%)	10 (48%)	7 (33%)	5 (24%)
Over 15	(12)	11 (91%)	9 (75%)	6 (50%)	5 (41%)
15 and under	(9)	3 (33%)	2 (22%)	1 (11%)	0 (0%)
"Classical"	(84)	33 (39%)	12 (14%)	6 (7%)	2 (2%)
Over 15	(26)	20 (77%)	9 (34%)	4 (15%)	1 (4%)
15 and under	(58)	13 (22%)	3 (5%)	2 (4%)	1 (2%)

108 months, respectively. Several medulloblastomas with extracranial metastases are reported in the literature.[6,7,26,28,30,37]

Two patients had meningiomas simultaneously with medulloblastoma; they lived 2 and 23 months, respectively.

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